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Synthesis of novel simplified sarcodictyin/eleutherobin analogs with potent microtubule-stabilizing activity, using ring closing metathesis as the key-step

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Abstract—The synthesis of a number of novel simplified eleutheside analogs with potent tubulin-assembling and microtubule-stabilizing properties is described, using ring closing metathesis as the key-step for obtaining the 6–10 fused bicyclic ring system. The RCM precursors were synthesized starting from aldehyde **3** [prepared in 6 steps on a multigram scale from *R*-(−)-carvone in 30% overall yield] via multiple stereoselective Brown allylations. Second generation RCM catalyst **13** gave the desired ring closed 10-membered carbocycles as single *Z* stereoisomers in good yields. The RCM stereochemical course (100% *Z*) likely reflects thermodynamic control. The crucial role of the protecting groups of the homoallylic and allylic substituents for the efficiency of the RCM reactions is discussed. These simplified analogs of the natural product (lacking inter alia the C-4/C-7 ether bridge) retain potent microtubule-stabilizing activity. However, the cytotoxicity tests did not parallel the potent tubulin-assembling and microtubule-stabilizing properties: limited cytotoxicity was observed against three common tumor cell lines (human ovarian carcinoma and human colon carcinoma cell lines, IC_{50} in the μM range given in Table 2), three orders of magnitude less than paclitaxel (IC_{50} in the nM range).

1. Introduction

Sarcodictyins A (**1a**) and B (**1b**) (Fig. 1) were isolated in 1987 by Pietra et al. from the Mediterranean stoloniferan coral *Sarcodictyon roseum*,[1] while their antitumor activity was recognized about a decade later, and their paclitaxel-like mechanism of action uncovered (1996).[2] In the meantime, the diterpene glycoside eleutherobin (**2**) was reported by Fenical et al. from an *Eleutherobia* species of australian soft coral, accompanied by disclosure of its potent cytotoxicity (1995).[3] Two years later, in 1997, it was shown that eleutherobin, similarly to sarcodictyins, acted by mitotic arrest through induced tubulin polymerization.[4] Both sarcodictyins and eleutherobin (the 'eleutheside' family of microtubule-stabilizing drugs) are characterized by an activity profile different from that of paclitaxel; in particular, they are active against paclitaxel resistant tumor cell lines and therefore hold potential as second generation microtubule-stabilizing anticancer agents.[4,5] The scarce availability of **1**–**2** from natural sources makes their total syntheses vital for further biological investigations.[5] To date, sarcodictyins A and B have been synthesized successfully by Nicolaou et al.,[6] who have also exploited a similar route for accessing eleutherobin.[7] A subsequent report by Danishefsky and co-workers details an elegant alternative access to eleutherobin.[8] A number of partial syntheses and approaches have also been described.[9]

The total syntheses of the eleuthesides have generated very

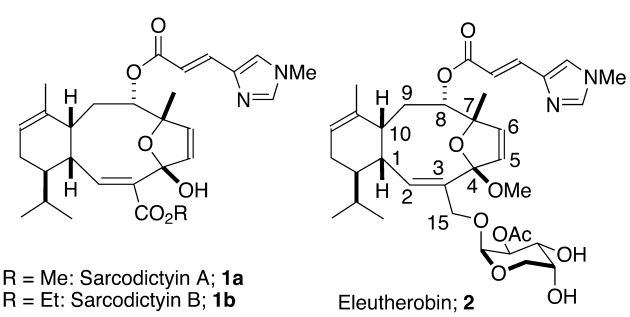

Figure 1. Marine diterpenoids sarcodictyin A (**1a**), B (**1b**) and eleutherobin (**2**).

Keywords: allylation; antitumor compounds; metathesis; stereocontrol.
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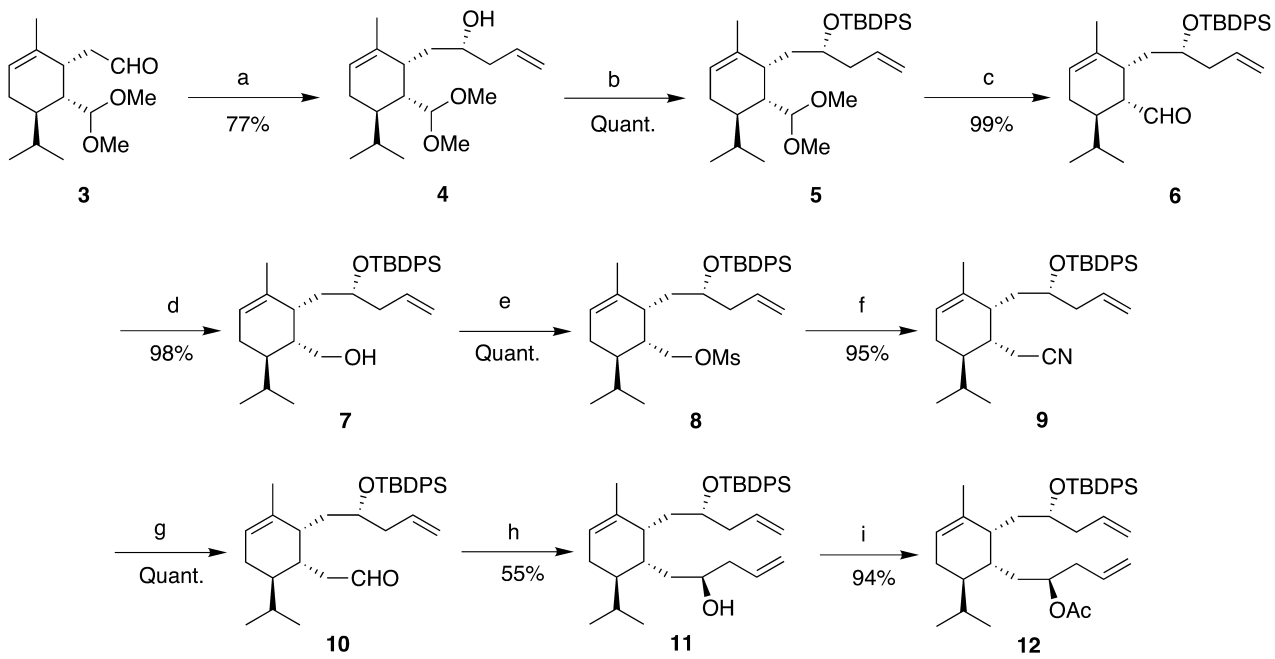


Scheme 1. *Reagents and conditions*: (a) (i) AllMgBr, $^{l}Ipc_2BOMe$, Et_2O-THF, 0°C to rt; (ii) **3**, −78°C to rt, 6 h; (iii) 6N NaOH, H_2O_2, rt, 15 h, 77% (>95% diastereomeric purity). (b) TBDPS–Cl, excess imidazole, CH_2Cl_2, rt, 16 h, quant. (c) AcOH/THF/H_2O (3:1:1), rt, 16 h, 99%. (d) $NaBH_4$, EtOH, rt, 15 min, 98%. (e) MsCl, Et_3N, CH_2Cl_2, 0°C to rt, 1 h, quant. (f) KCN, 18-crown-6, MeCN, 80°C, 5 h, 95%. (g) DIBAl-H, hexane/toluene (2:1), −78°C, 40 min, quant. (h) (i) AllMgBr, $^{l}Ipc_2BOMe$, Et_2O-THF, 0°C to rt; (ii) **10**, −78°C to rt, 3 h; (iii) 6N NaOH, H_2O_2, rt, 15 h, 55% (>95% diastereomeric purity). (i) Ac_2O, cat. DMAP, Py, rt, 94%.

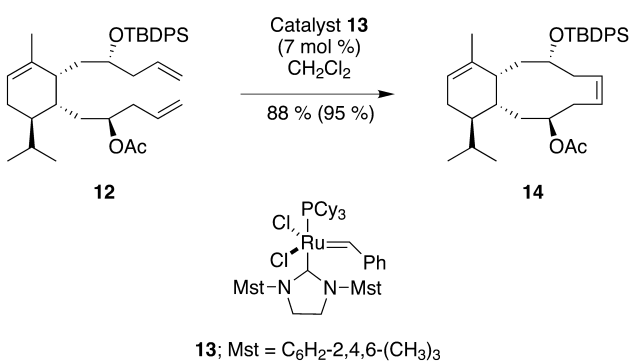
limited diversity in the diterpenoid core, with major variations reported only in the C-15 functionality and C-8 side-chain.[5–8] As part of our ongoing program aimed at the synthesis of simplified analogs of the eleutheside natural products, ideally showing improved synthetic accessibility and retaining microtubule-stabilizing properties, we describe in this full account of our work the synthesis of a number of eleutheside analogs with potent tubulin-assembling and microtubule-stabilizing activity, using ring closing metathesis (RCM) as the key-step for obtaining the 6–10 fused bicyclic ring system.[10] We also report the cytotoxicity tests (IC_{50} values) performed on these compounds using several different tumor cell lines.

2. Results and discussion

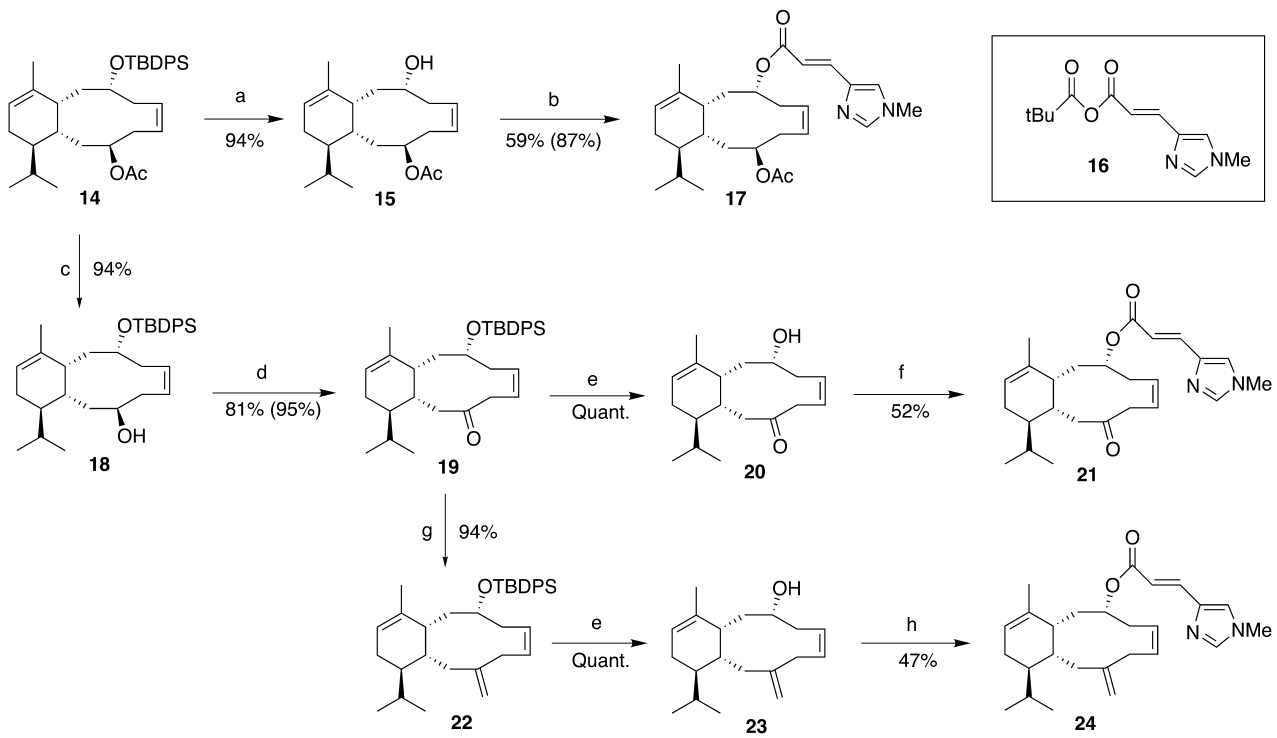
Aldehyde **3** (prepared in 6 steps on a multigram scale from *R*-(−)-carvone in 30% overall yield)[9a,g] was submitted to the allyl borane derived from (−)-α-pinene,[11] generating the homoallylic oxygenated stereocenter (alcohol **4**, Scheme 1).

The allylation reaction proceeded with complete stereocontrol in favor of the desired stereoisomer (diastereomeric purity >95% by ^1H- and ^{13}C NMR). After standard alcohol protection, an efficient and well established sequence of steps[8c] led to the homologated aldehyde **10**, on which the same allylation procedure described above was applied. Addition of the allyl borane derived from (−)-α-pinene to aldehyde **10** was again completely stereoselective (diastereomeric purity of **11** >95%). Homoallylic alcohol **11** was acetylated to **12**, and this diene was subjected to ring closing metathesis[12] using a variety of catalysts. After a number of attempts, the 'second generation' RCM-catalyst[13] **13** gave the desired ring closed product **14** as a single *Z* stereoisomer in 88% yield (95% considering the recovered starting material, Scheme 2).

As expected, entropic support (by virtue of the *cis* fusion to the cyclohexyl ring) made ring closure of diene **12** extremely smooth. Despite the known effectiveness of RCM in the synthesis of rings of all sizes, no control over the *E*/*Z* stereochemistry of the double bond generated is usually possible for ring sizes >8.[12] Luckily, and delightfully, the stereochemistry of the double bond created by this RCM reaction was fully controlled in the desired sense (100% *Z*) by the structure of the new 10-membered carbocycle.[14] This stereochemical course, which was found to be common to the cyclization of all the substrates reported in the present manuscript (vide infra), likely reflects thermodynamic control.[15] The *Z* stereochemistry of the double bond was unequivocally assigned by detection of the olefinic $^3J_{cis}$ coupling constant (11.5 Hz between the protons at δ=5.51 and 5.86 ppm, respectively) in a 400 MHz H,H-COSY



Scheme 2.



Scheme 3. *Reagents and conditions*: (a) TBAF, THF, rt, 94%. (b) **16** (Ref. 6b), Et_3N, DMAP, CH_2Cl_2, 59% (87% considering the recovered starting material). (c) K_2CO_3, MeOH, 94%. (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60 to 0°C, 81% (95% considering the recovered starting material). (e) TBAF, THF, rt, quant. (f) **16** (Ref. 6b), Et_3N, DMAP, CH_2Cl_2, 52%. (g) $Ph_3P{=}CH_2$, THF, 50°C, 94%. (h) **16** (Ref. 6b), Et_3N, DMAP, CH_2Cl_2, 47%.

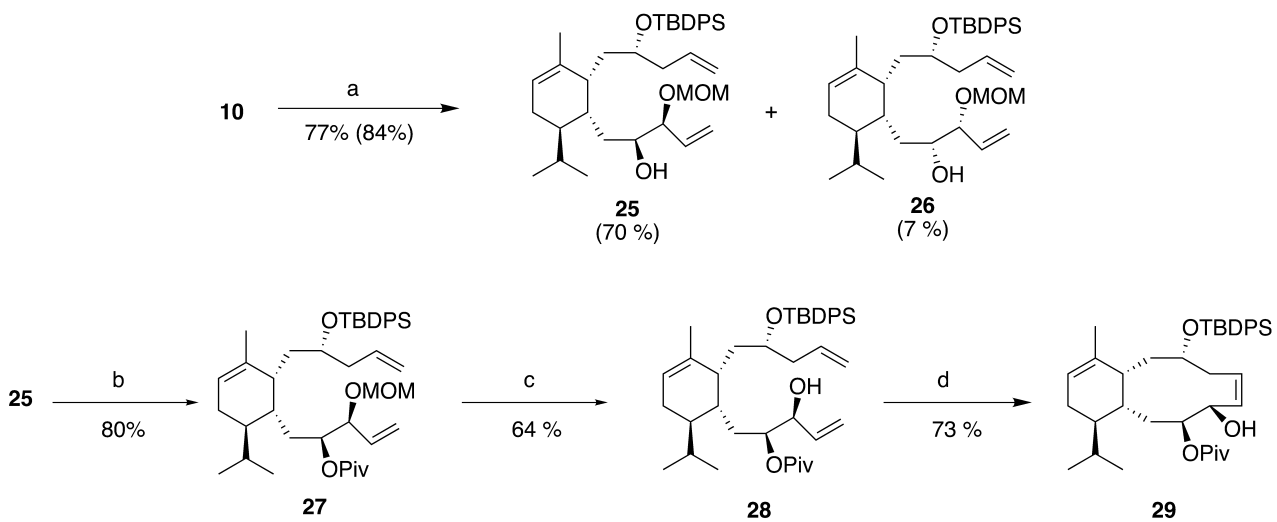
experiment, and by detection of a NOE contact between these protons in a 400 MHz NOESY experiment.

A first series of simple eleutheside analogs (**17**, **21** and **24**) was then synthesized from compound **14** using standard, high-yielding transformations (Scheme 3).

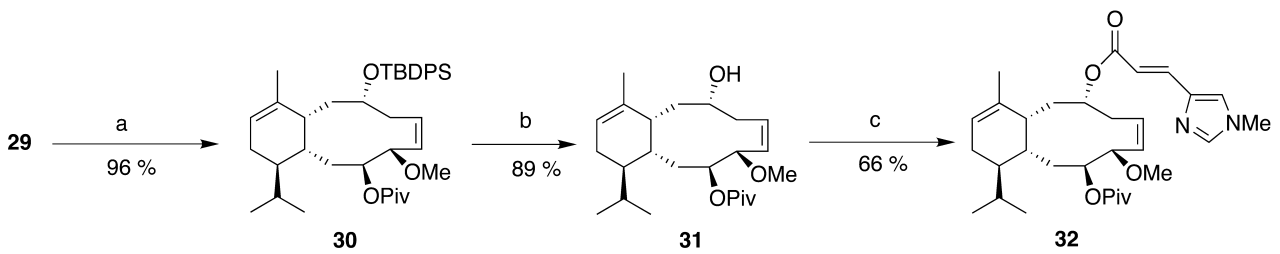
With the goal of synthesizing more functionalized eleutheside analogs, aldehyde **10** was oxyallylated using Brown's methodology [(*Z*)-γ-(methoxymethoxy) allyldiisopinocampheyl-borane from (−)-α-pinene][11d] in high yield (77%) and with good stereoselectivity (**25**/**26**=91:9, Scheme 4).

The major diastereomer **25** was isolated by flash chromatography and transformed into the allylic alcohol **28** via a simple protection/deprotection sequence. Second generation RCM catalyst **13**[13] gave the desired ring closed product **29** as a single *Z* stereoisomer in 73% yield.

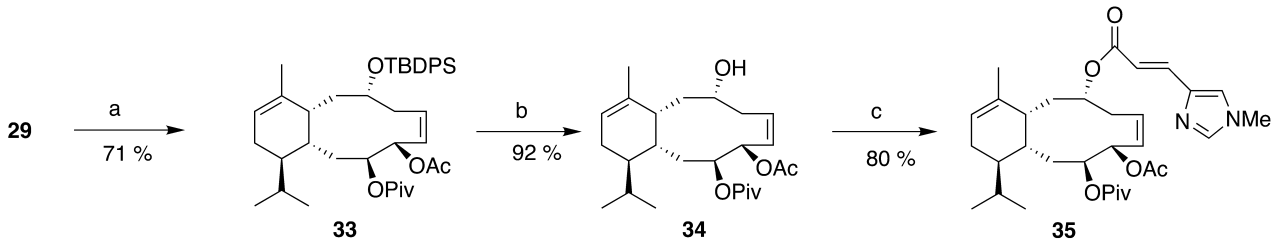
The reports that describe application of the RCM to medium sized—particularly ten-membered—rings, are still very rare, especially when dense functionality close to the reaction centre is involved.[14,16] The crucial role of the protecting groups in the cyclization precursor **28** is noteworthy: (a) the large TBDPS group in the homoallylic



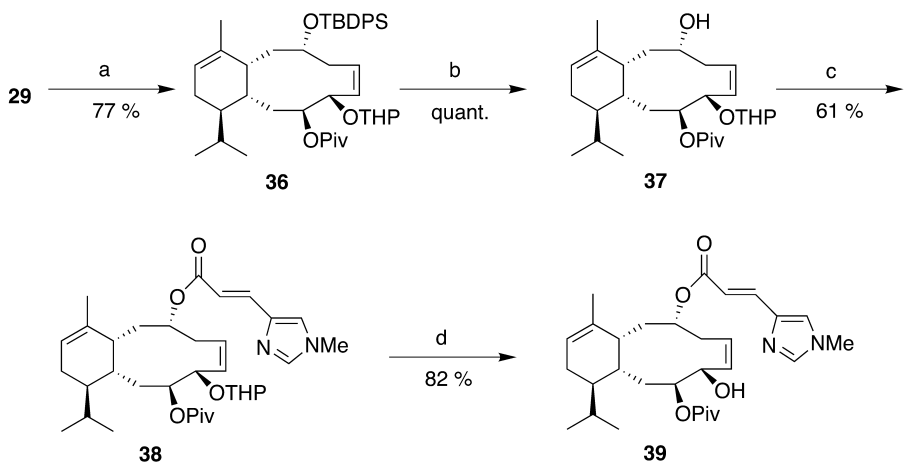
Scheme 4. *Reagents and conditions*: (a) (i) $^{t}Ipc_2BOMe$, AllO-MOM, *s*-BuLi, $BF_3{\cdot}Et_2O$, THF, −78°C; (ii) 6N NaOH, H_2O_2, rt, 15 h, 77% (84% considering the recovered starting material, de=82%, **25**/**26**=10:1). (b) *t*-BuCOCl (PivCl), cat. DMAP, Py, rt, 80%. (c) $BF_3{\cdot}Et_2O$, PhSH, CH_2Cl_2, −78 to −10°C, 64%. (d) **13** (9 mol%), CH_2Cl_2, rt, 120 h, 73% (100% *Z*).



Scheme 5. *Reagents and conditions*: (a) MeOTf, 2,6-di-*t*-Bu-Py, CH_2Cl_2, 40°C, 96%. (b) TBAF, THF, rt, 89%. (c) **16** (Ref. 6b), Et_3N, DMAP, CH_2Cl_2, 66%.



Scheme 6. *Reagents and conditions*: (a) Ac_2O, cat. DMAP, Py, rt, 71%. (b) TBAF, THF, rt, 92%. (c) **16** (Ref. 6b), Et_3N, DMAP, CH_2Cl_2, 80%.



Scheme 7. *Reagents and conditions*: (a) DHP, PPTS, CH_2Cl_2, 77%. (b) TBAF, THF, rt, quant. (c) **16** (Ref. 6b), Et_3N, DMAP, CH_2Cl_2, 61%. (d) PTSA, $EtOH/H_2O$ (8:2), 82%.

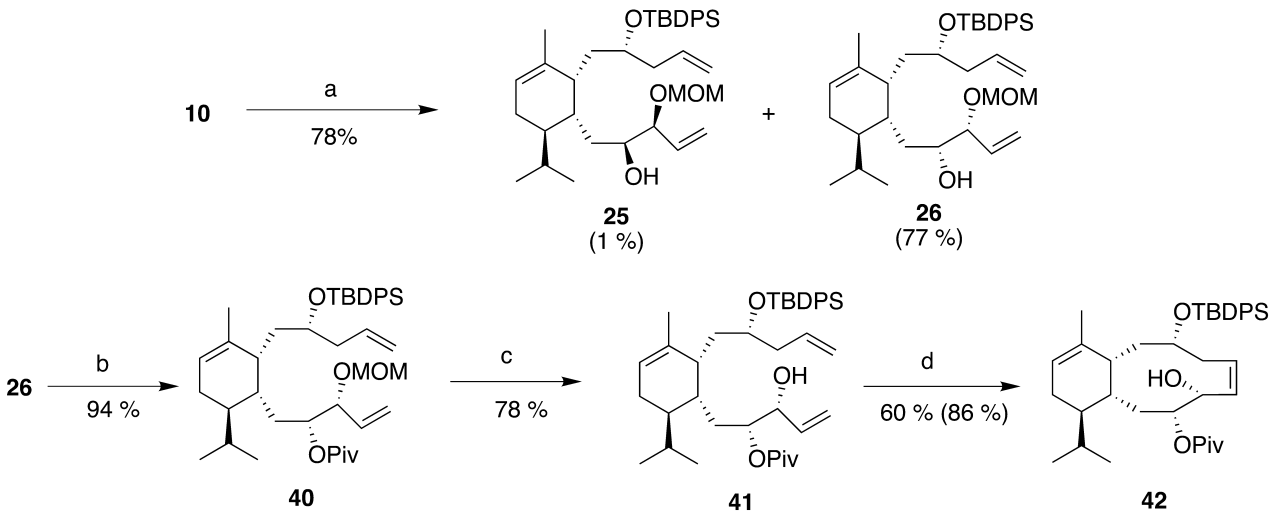
position helps to suppress the undesired dimerization reaction;[17] (b) a free alcohol[18] in the allylic position is important to promote the cyclization (the RCM reaction did not occur on dienes with variously protected alcohols in the allylic position, e.g. OMe, OMOM).[19]

Compound **29** was transformed into a second set of eleutheside analogs **32**, **35** and **39**, using standard, high-yielding transformations (Schemes 5–7).

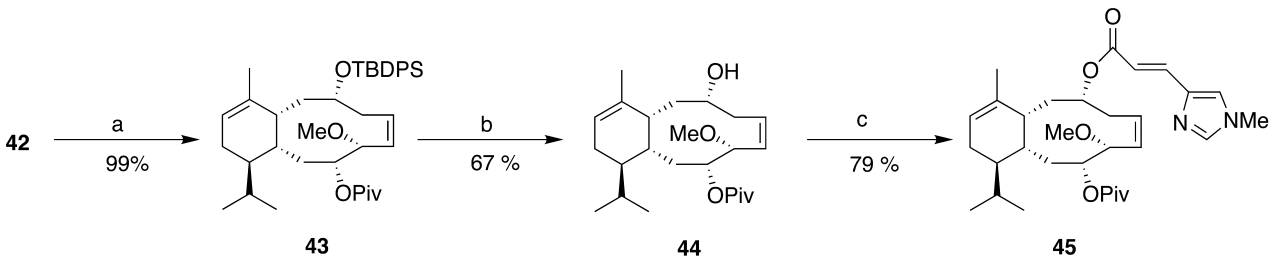
Aldehyde **10** was also oxyallylated using Brown's enantiomeric reagent [(*Z*)-γ-(methoxymethoxy)allyldiisopinocampheyl-borane from (+)-α-pinene][11d] in high yield (78%) and with excellent stereoselectivity (**26/25**= 98.7:1.3, Scheme 8). The major diastereomer **26** was isolated by flash chromatography and transformed into the allylic alcohol **41** via a simple protection/deprotection sequence (in this case Me_2S, $BF_3{\cdot}Et_2O$ proved more reliable than PhSH, $BF_3{\cdot}Et_2O$ for deprotecting the allylic alcohol from the MOM group).[20] Treatment with catalyst **13** gave the desired ring closed product **42** as a single *Z* stereoisomer in 60% yield. By comparing this RCM reaction with the one described above leading to **29**, a relatively minor effect of the stereochemistry of the homoallylic and allylic substituents on the RCM performance can be observed.[21] Finally, a standard sequence of reactions transformed compound **42** into the eleutheside analogs **45** and **49** (Schemes 9 and 10).

The effect of these new eleutheside analogs on the assembly of tubulin and on the stability of the formed microtubules was assessed at Pharmacia (Nerviano, Italy) and at Salford (UK), using the potent microtubule-stabilizing agent paclitaxel as a reference (Table 1).[2b]

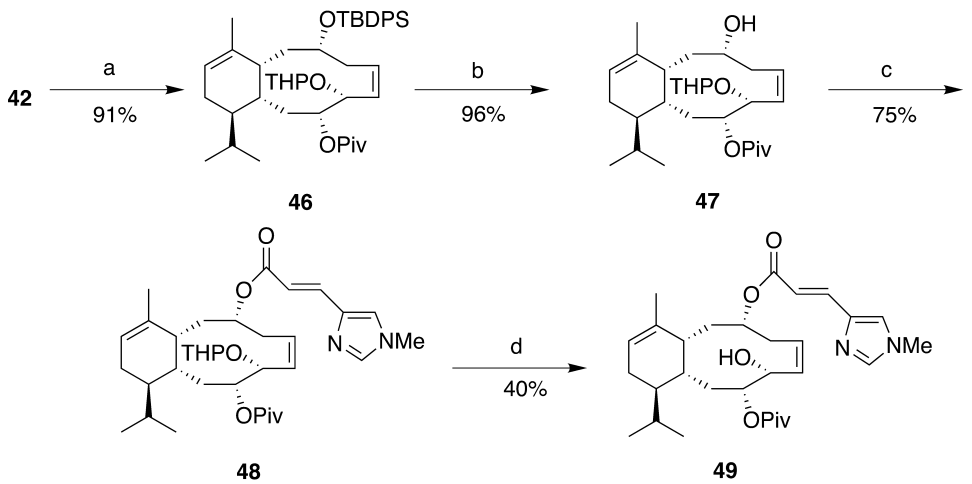
Eleutheside analogs **21** and **45** were shown to be at least as



Scheme 8. *Reagents and conditions*: (a) (i) $^{d}Ipc_2BOMe$, AllO-MOM, *s*-BuLi, $BF_3{\cdot}Et_2O$, THF, −78°C; (ii) H_2O_2, 6N NaOH, rt, 15 h, 78% (de=97.4%, **25**/**26**=1.3:98.7). (b) *t*-BuCOCl (PivCl), cat. DMAP, Py, rt, 94%. (c) $BF_3{\cdot}Et_2O$, Me_2S, CH_2Cl_2, −20°C, 78%. (d) **13** (10 mol%), CH_2Cl_2, rt, 120 h, 60% (86% considering the recovered starting material, 100% *Z*).



Scheme 9. *Reagents and conditions*: (a) MeOTf, 2,6-di-*t*-Bu-Py, CH_2Cl_2, 40°C, 99%. (b) TBAF, THF, rt, 67%. (c) **16** (Ref. 6b), Et_3N, DMAP, $ClCH_2CH_2Cl$, 79%.



Scheme 10. *Reagents and conditions*: (a) DHP, PPTS, CH_2Cl_2, 91%. (b) TBAF, THF, rt, 96%. (c) **16** (Ref. 6b), Et_3N, DMAP, CH_2Cl_2, 75%. (d) PTSA, $EtOH/H_2O$ (8:2), 40%.

Table 1. Tubulin polymerizing activities

Compound	ED_{50} (μM)	ED_{90} (μM)	Paclitaxel ED_{50} (μM)	Paclitaxel ED_{90} (μM)
17	2.0	10.0	<0.5	0.5
21	0.2	1.2	0.5	3.0
24	5.0	16.0	<0.5	0.5
32	3.0	7.0	0.5	3.0
35	1.0	1.7	<0.5	0.5
39	1.0	1.8	<0.5	0.5
45	<0.5	1.0	<0.5	1.0
49	<0.5	3.0	<0.5	1.0

ED_{50}, effective dose that induces 50% tubulin polymerization; ED_{90}, effective dose that induces 90% tubulin polymerization (see Ref. 2b). ED values may vary depending on the tubulin batch (from pig brain): the same batch is used for the paclitaxel reference assay.

Table 2. Cytotoxicity assays: IC_{50} values on A2780, HCT116, HT29 tumor cell lines

Compound	IC_{50} (μM) (A2780)	IC_{50} (μM) (HCT116)	IC_{50} (μM) (HT29)
17	4[a]	12[b]	n.d.[c]
21	40[a]	35–60[b]	30[a]
24	4[a]	5[b]	6[a]
32	<5[a]	10–25[b]	7[a]
35	n.d.[c]	n.d.[c]	n.d.[c]
39	4[a]	4[b]	5[a]
45	10[a]	7[b]	n.d.[c]
49	10[a]	7[b]	n.d.[c]

IC_{50} values: concentration inhibiting cell growth by 50%. A2780: human ovarian carcinoma cell line. HCT116 and HT29: human colon carcinoma cell lines.
[a] Paclitaxel $IC_{50}<5$ nM.
[b] Paclitaxel $IC_{50}\leq 5$ nM.
[c] Not determined.

potent as paclitaxel. Microtubules were generated in the presence of $CaCl_2$ at 37°C and were stable (did not depolymerize) at 10°C. Although there is a general agreement that the (*E*)-*N*-methylurocanic side chain, the C-4/C-7 ether bridge, and the cyclohexene ring are important determinants of antimitotic activity,[5] it is interesting to note that these simplified analogs of the natural product (lacking inter alia the C-4/C-7 ether bridge) retain potent microtubule-stabilizing activity. Given the dramatic impact that the furanose oxygen deletion is likely to have on the conformation of the ring system, the fact that some of these compounds retain activity comparable to paclitaxel in the tubulin polymerization assay is remarkable.

However, the cytotoxicity assays did not parallel the potent tubulin-assembling and microtubule-stabilizing properties: limited cytotoxicity was observed against three common tumor cell lines (human ovarian carcinoma and human colon carcinoma cell lines, IC_{50} in the μM range, Table 2), three orders of magnitude less than paclitaxel (IC_{50} in the nM range). This might be due to an easy esterase-mediated hydrolytic cleavage of the *N*-methylurocanic ester side-chain in living cells (it is known that the natural eleuthesides are devoid of any cytotoxicity when the *N*-methylurocanic ester side-chain is lacking in position 8).[5] Natural eleutheosides have a fully substituted quaternary carbon in position 7, adjacent to the ester, which is likely to hinder its hydrolysis.

Work is in progress to synthesize more potent eleutheside analogs (substituted at C-7), investigate the interaction with tubulin and establish their cytotoxicity.

3. Experimental

3.1. General procedures

All reactions were carried out in flame-dried glassware under argon atmosphere. All commercially available reagents were used as received. The solvents were dried by distillation over the following drying agents and were transferred under nitrogen: CH_3CN (CaH_2), CH_2Cl_2 (CaH_2), THF (Na), Et_2O (Na). Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} precoated glass plates (0.25 mm thickness). TLC R_f values are reported. Visualization was accomplished by irradiation with a UV lamp and/or staining with ceric ammonium molybdate (CAM) solution. Flash column chromatography was performed using silica gel 60 Å, particle size 40–64 μm. Proton NMR spectra were recorded on 400, 300, or 200 MHz spectrometers. Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ 7.26 ppm; d_6-DMSO δ 2.50 ppm). Carbon NMR spectra were recorded on 400 (100 MHz), 300 (75 MHz) or 200 (50 MHz) spectrometers with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ 77.0). Infrared spectra were recorded on a standard Infrared Spectrophotometer; peaks are reported in cm^{-1}. Optical rotation values were measured on an automatic polarimeter at the sodium D line. High resolution mass spectra (HRMS) were performed on a hybrid quadrupole time of flight mass spectrometer equipped with an ESI ion source. A Reserpine solution 100 pg/μL (about 100 counts/s), 0.1% HCOOH/CH_3CN 1:1, was used as reference compound (Lock Mass).

3.1.1. (2*R*)-1-[(1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enyl]-pent-4-en-2-ol (4). To AllMgBr (0.61 mL, 0.61 mmol, 1.0 M in Et_2O) was slowly added $^{l}Ipc_2BOMe$ (0.83 mL, 0.71 mmol, 0.86 M in THF) at 0°C. The mixture was stirred at ambient temperature for 1 h, then cooled to −78°C and aldehyde **3** [prepared from *R*-(−)-carvone in 30% overall yield according to Ref. 9g; 149 mg, 0.51 mmol] in THF (2 mL) was added. The reaction mixture was stirred at −78°C for 6 h, warmed to room temperature and an aqueous NaOH solution (0.25 mL, 6.0 M) and H_2O_2 (0.20 mL, 35%) were added. The mixture was stirred at room temperature overnight. The layers were separated, the aqueous layer was extracted with Et_2O (3×10 mL) and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 4:1) to give compound **4** (117 mg, 77%, de≥95%) as a colorless oil. R_f=0.43 (hexane/EtOAc 4:1); ^1H NMR (200 MHz, $CDCl_3$): δ=5.98–5.77 (m, 1H), 5.36 (m, 1H), 5.16–5.12 (m, 1H), 5.07 (br s, 1H), 4.36 (d, *J*=5.4 Hz, 1H), 3.95–3.86 (m, 1H), 3.38 (s, 6H), 2.46–1.19 (m, 14H), 0.94 (d, *J*=6.6 Hz, 3H), 0.84 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=136.7, 135.6, 121.1, 116.8, 106.9, 68.4, 54.7, 54.4, 42.9, 40.2, 37.1, 36.0, 34.7, 27.0, 24.4, 22.2, 21.0, 17.1; IR (CCl_4): ν=3590, 3480, 3064, 2945, 2919, 2820, 1516, 1457, 1438, 1380, 1361, 1155, 1105, 1065, 910; $[\alpha]_D^{20}$=+63.6 (*c*=1.16, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{18}H_{32}NaO_3$: 319.2249 $[M+Na]^+$; found: 319.2241.

3.1.2. *tert*-Butyl-{(1*R*)-1-[(1*R*,5*R*,6*R*)-6-dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enyl-methyl]-but-3-enyloxy}-diphenyl-silane (5). Alcohol **4** (184 mg, 0.62 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0°C. Imidazole (211 mg, 3.11 mmol) and TBDPSCl (341 mg, 1.24 mmol) were added. The reaction mixture stirred for 90 min at 0°C and at room temperature overnight. The solvent was evaporated under reduced pressure and the

residue was purified by flash chromatography (hexane/EtOAc 25:1) to yield compound **5** (332 mg, quant.) as a colorless oil. R_f=0.40 (hexane/EtOAc 25:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.78–7.76 (m, 4H), 7.72–7.49 (m, 6H), 5.76–5.59 (m, 1H), 5.24 (m, 1H), 4.90–4.73 (m, 2H), 4.09 (d, J=5.6 Hz, 1H), 4.06–3.98 (m, 1H), 3.19 (s, 3H), 3.17 (s, 3H), 2.47–2.41 (m, 1H), 2.14–2.07 (m, 2H), 1.93–1.72 (m, 6H), 1.65 and 1.64 (s, 3H), 1.42–1.22 (m, 1H), 1.06 (s, 9H), 0.84 (d, J=6.8 Hz, 3H), 0.75 (d, J=6.6 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=138.6, 136.1 (2C), 136.0 (2C), 135.3, 135.1, 134.8, 129.2 (2C), 127.3 (2C), 127.2 (2C), 120.5, 116.1, 107.6, 72.5, 54.7, 54.6, 42.3, 41.3, 38.1, 35.5, 35.1, 27.1, 27.1 (3C), 24.1, 22.9, 21.5, 19.4, 16.3; IR (CCl_4): ν=3060, 3040, 2943, 2917, 2840, 1465, 1420, 1381 1320, 1105, 1075, 905; $[\alpha]_D^{20}$=+46.4 (c=1.04, EtOAc); HRMS (ESI): m/z: calcd for $C_{34}H_{50}NaO_3Si$: 557.3427 $[M+Na]^+$; found: 557.3413.

3.1.3. {(1*R*,2*R*,6*R*)-2-[(2*R*)-2-(*tert*-Butyl-diphenyl-silanyl-oxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-ene}-carbaldehyde (6). Compound **5** (332 mg, 0.62 mmol) was dissolved in a mixture of AcOH/H_2O/THF (15 mL, v/v/v, 3:1:1) and stirred at room temperature for 21 h. The solution was transferred to a separatory funnel charged with a saturated aqueous $NaHCO_3$ solution (30 mL). Solid $NaHCO_3$ was added until no more gas was evolved and the solution was neutralized to pH=7. EtOAc (20 mL) was added and after separation of the layers, the aqueous layer was extracted with EtOAc (3×20 mL) and the combined organic extracts were dried over Na_2SO_4. Evaporation of the solvent under reduced pressure yielded pure aldehyde **6** (299 mg, 99%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ=9.55 (d, J=3.6 Hz, 1H), 7.71–7.58 (m, 4H), 7.48–7.29 (m, 6H), 5.72–5.51 (m, 1H), 5.30 (m, 1H), 4.99–4.79 (m, 2H), 3.79–3.69 (m, 1H), 2.43–1.01 (m, 22H), 0.88 (d, J=6.7 Hz, 3H), 0.74 (d, J=6.6 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=206.5, 136.1, 135.9 (4C), 134.2, 134.1, 134.0, 129.7, 129.6, 127.6 (2C), 127.5 (2C), 121.6, 117.5, 72.1, 53.1, 41.6, 36.9, 35.7, 35.3, 27.1 (3C), 26.3, 23.8, 22.3, 20.6, 19.3, 16.9; IR (CCl_4): ν=3060, 2945, 2918, 2842, 2700, 1713, 1465, 1458, 1420, 1382, 1363, 1105, 1061, 910; $[\alpha]_D^{20}$=+28.4 (c=1.22, EtOAc); HRMS (ESI): m/z: calcd for $C_{32}H_{44}NaO_2Si$: 511.3008 $[M+Na]^+$; found: 511.2996.

3.1.4. {(1*R*,2*R*,6*R*)-2-[(2*R*)-2-(*tert*-Butyl-diphenyl-silanyl-oxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enyl}-methanol (7). Aldehyde **6** (834 mg, 1.71 mmol) was dissolved in EtOH (7 mL) and $NaBH_4$ (129 mg, 3.41 mmol) was added. The reaction mixture was stirred at room temperature for 15 min. Solid NH_4Cl (919 mg) was then added and the mixture was stirred for 30 min, was then diluted with Et_2O and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 25:1) to yield alcohol **7** (818 mg, 98%) as a colorless oil. R_f=0.21 (hexane/EtOAc 25:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.77–7.57 (m, 4H), 7.45–7.34 (m, 6H), 5.92–5.75 (m, 1H), 5.26 (br s, 1H), 5.05–4.92 (m, 2H), 4.08–3.95 (m, 1H), 3.65 (dd, J=10.9, 5.6 Hz, 1H), 3.48–3.38 (m, 1H), 2.30 (t, J=5.8 Hz, 2H), 1.90–0.91 (m, 21H), 0.85 (d, J=6.8 Hz, 3H), 0.79 (d, J=6.8 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=137.4, 136.0 (4C), 135.2, 134.7, 134.4, 129.6 (2C), 127.5 (4C), 121.5, 117.2, 72.3, 62.4, 41.7, 41.3, 36.9, 36.0, 34.7, 27.1 (4C), 24.1, 23.4, 21.2, 19.4, 16.2; IR (CCl_4): ν=3615, 3060, 2945, 2918, 2880, 2842, 1422, 1381, 1363, 1105, 1058; $[\alpha]_D^{20}$=+67.5 (c=0.99, EtOAc); HRMS (ESI): m/z: calcd for $C_{32}H_{47}O_2Si$: 491.3345 $[M+H]^+$; found: 491.3341.

3.1.5. Methanesulfonic acid {(1*R*,2*R*,6*R*)-(2-[(2*R*)-2-(*tert*-butyl-diphenyl-silanyloxy)-pent-4-enyl]-6-iso-propyl-3-methyl-cyclohex-3-enyl}-methyl ester (8). Alcohol **7** (218 mg, 0.44 mmol) was dissolved in CH_2Cl_2 (4 mL) and cooled to 0°C. NEt_3 (135 mg, 1.33 mmol) and MsCl (76 mg, 0.66 mmol) were added. The reaction mixture was stirred for 1 h at 0°C and for 1 h at room temperature. The solvent was evaporated under reduced pressure and the residue was taken up in EtOAc (10 mL) and H_2O (10 mL). The aqueous layer was extracted with EtOAc (3×10 mL) and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 4:1) to yield mesylate **8** (250 mg, quant.) as a colorless oil. R_f=0.63 (hexane/EtOAc 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.65–7.59 (m, 4H), 7.44–7.30 (m, 6H), 5.88–5.67 (m, 1H), 5.23 (br s, 1H), 5.02–4.88 (m, 2H), 4.21 (dd, J=10.0, 6.5 Hz, 1H), 3.98 (dd, J=10.0, 8.5 Hz, 2H), 2.86 (s, 3H), 2.31–2.26 (m, 3H), 2.04–0.99 (m, 19H), 0.82 (d, J=6.0 Hz, 3H), 0.80 (d, J=6.0 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=136.3, 135.9 (4C), 134.7, 134.4 (2C), 129.6 (2C), 127.6 (4C), 121.5, 117.5, 72.1, 70.1, 41.3, 39.0, 37.3, 37.0, 36.3, 34.8, 27.3, 27.1 (3C), 23.7, 23.2, 21.0, 19.4, 17.0; IR (CCl_4): ν=3070, 2960, 2930, 2858, 1471, 1428, 1389, 1368, 1348, 1329, 1180, 1110, 1062; $[\alpha]_D^{20}$=+58.1 (c=0.92, EtOAc); HRMS (ESI): m/z: calcd for $C_{33}H_{52}NO_4SiS$: 586.3386 $[M+NH_4]^+$; found: 586.3368.

3.1.6. {(1*R*,2*R*,6*R*)-2-[(2*R*)-2-(*tert*-Butyl-diphenyl-silanyl-oxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enyl}-acetonitrile (9). Compound **8** (162 mg, 0.29 mmol), KCN (56 mg, 0.86 mmol) and 18-crown-6 (226 mg, 0.86 mmol) were dissolved in CH_3CN (3 mL). The reaction mixture was heated to 80°C for 6 h. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 14:1) to yield compound **9** (136 mg, 95%) as a colorless oil. R_f=0.40 (hexane/EtOAc 14:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.71–7.69 (m, 4H), 7.47–7.33 (m, 6H), 5.84–5.70 (m, 1H), 5.22 (br s, 1H), 5.05–4.92 (m, 2H), 3.95–3.86 (m, 1H), 2.27–1.27 (m, 15H), 1.05 (s, 9H), 0.83 (d, J=6.8 Hz, 3H), 0.79 (d, J=6.8 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=135.8 (4C), 135.4, 134.3, 134.2, 134.1, 129.5 (2C), 127.4 (4C), 121.2, 119.4, 117.6, 71.8, 40.9, 38.5, 36.3, 36.1, 35.9, 27.2, 27.0 (3C), 23.4, 22.8, 20.8, 19.2, 17.8, 17.5; IR (CCl_4): ν=3070, 2955, 2922, 2890, 2856, 1715, 1470, 1460, 1425, 1388, 1369, 1110, 1070, 915; $[\alpha]_D^{20}$=+66.4 (c=1.28, EtOAc); HRMS (ESI): m/z: calcd for $C_{33}H_{45}NaNOSi$: 522.3168 $[M+Na]^+$; found: 522.3179.

3.1.7. {(1*R*,2*R*,6*R*)-2-[(2*R*)-2-(*tert*-Butyl-diphenyl-silanyl-oxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enyl}-acetaldehyde (10). Compound **9** (185 mg, 0.37 mmol) was dissolved in toluene/*n*-hexane (6 mL, v/v, 1:2) and cooled to −78°C. DIBAL-H (3.7 mL, 3.70 mmol, 1.0 M in hexanes) was added and the solution was stirred for 45 min at −78°C. EtOAc (3 mL) and an aqueous tartaric

acid solution (3 mL, 1.0 M) were added and the mixture was warmed to room temperature and stirred for 1 h at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3×5 mL), the combined organic extracts were washed with an aqueous Na,K-tartrate solution (2×5 mL, 1.0 M) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 14:1) to yield aldehyde **10** (186 mg, quant.) as a colorless oil. R_f=0.39 (hexane/EtOAc 14:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=9.66 (s, 1H), 7.78–7.71 (m, 4H), 7.45–7.35 (m, 6H), 5.91–5.71 (m, 1H), 5.26 (br s, 1H), 5.07–4.90 (m, 2H), 3.91 (q, J=5.9 Hz, 1H), 2.38–2.03 (m, 5H), 1.99–0.93 (m, 19H), 0.87 (d, J=6.7 Hz, 3H), 0.75 (d, J=6.7 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=203.1, 136.6, 135.9 (4C), 134.6, 134.5, 134.3, 129.6 (2C), 127.5 (4C), 121.3, 117.4, 72.1, 44.2, 41.2, 38.9, 37.0, 36.4, 34.3, 27.4, 27.1 (3C), 23.7, 23.1, 21.2, 19.4, 17.2; IR (CCl_4): ν=3060, 2943, 2917, 2880, 2842, 2695, 1720, 1465, 1455, 1420, 1382, 1365, 1103, 1095, 1060, 910; $[\alpha]_D^{20}$=+53.3 (c=1.14, EtOAc).

3.1.8. (2*R*)-1-{(1*R*,2*R*,6*R*)-2-[(2*R*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enyl}-pent-4-en-2-ol (11). To AllMgBr (0.15 mL, 0.15 mmol, 1.0 M in Et_2O) ^{1}Ipc$_2$BOMe was added (0.17 mL, 0.17 mmol, 1.0 M in THF) at 0°C. The mixture was stirred at room temperature for 1 h, then cooled to −78°C and a solution of aldehyde **10** (25 mg, 0.05 mmol) in THF (0.2 mL) was added. The mixture was stirred at −78°C for 3 h, then warmed to room temperature and an aqueous NaOH solution (0.25 mL, 6.0 M) and H_2O_2 (0.20 mL, 35%) were added. Stirring was continued at ambient temperature for 40 min, then H_2O (5 mL) and Et_2O (10 mL) were added. The aqueous layer was extracted with Et_2O (3×5 mL) and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 4:1) to yield compound **11** (15 mg, 55%, de≥95% by ^{1}H- and ^{13}C NMR) as a colorless oil. R_f=0.59 (hexane/EtOAc 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.73–7.56 (m, 4H), 7.46–7.27 (m, 6H), 5.91–5.70 (m, 2H), 5.49–4.92 (m, 5H), 4.17–3.89 (m, 1H), 3.67–3.62 (m, 1H), 2.51–1.92 (m, 5H), 1.82–1.19 (m, 13H), 1.09 (s, 9H), 0.82 (d, J=6.7 Hz, 3H), 0.76 (d, J=6.7 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=136.9, 135.9 (4C), 135.0, 134.9, 134.6, 134.5, 129.5 (2C), 127.4 (4C), 121.1, 118.0, 117.0, 72.2, 68.3, 41.9, 41.5, 38.5, 37.1, 35.8, 35.4, 35.2, 27.1, 27.0 (3C), 23.9, 23.1, 21.2, 19.3, 17.5; IR (CCl_4): ν=3595, 3078, 2960, 2934, 2899, 2860, 1642, 1475, 1465, 1430, 1389, 1371, 1110, 1069, 917; $[\alpha]_D^{20}$=+38.8 (c=0.84, EtOAc); HRMS (ESI): m/z: calcd for $C_{36}H_{52}NaO_2Si$: 567.3634 $[M+Na]^+$; found: 567.3665.

3.1.9. Acetic acid {(1*R*)-1-{(1*R*,2*R*,6*R*)-2-[(2*R*)-2-(*tert*-butyl-diphenyl-silanyloxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enylmethyl}-but-3-enyl} ester (12). Compound **11** (234 mg, 0.43 mmol) was dissolved in pyridine (1.5 mL). Ac_2O (88 mg, 0.86 mmol) and DMAP (6 mg, 0.05 mmol) were added and the reaction mixture was stirred for 24 h at room temperature. EtOAc (20 mL) was added and the organic layer was washed with a saturated aqueous $KHSO_4$ solution (2×15 mL), the aqueous layer was back extracted with EtOAc (3×20 mL) and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 14:1) to give compound **12** (237 mg, 94%) as a colorless oil. R_f=0.58 (hexane/EtOAc 14:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.99–7.65 (m, 4H), 7.45–7.28 (m, 6H), 5.91–5.62 (m, 2H), 5.19–4.87 (m, 6H), 3.91 (q, J=5.7 Hz, 1H), 2.30–2.01 (m, 5H), 1.97 (s, 3H), 1.85–1.14 (m, 11H), 1.06 (s, 9H), 0.95–0.84 (m, 1H), 0.76 (d, J=6.6 Hz, 3H), 0.72 (d, J=6.6 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=170.4, 135.8 (4C), 135.0, 134.5, 134.4 (2C), 133.6, 129.4 (2C), 127.3 (4C), 121.1, 117.6, 117.0, 71.9, 71.2, 41.4, 39.2, 39.0, 36.6, 34.8, 33.5, 31.5, 27.2, 27.0 (3C), 23.6, 22.9, 21.1, 20.9, 19.3, 19.2; IR (CCl_4): ν=3050, 2934, 2911, 2831, 1726, 1460, 1450, 1415, 1375, 1359, 1096, 1090, 1052, 900; $[\alpha]_D^{20}$=+27.9 (c=1.26, EtOAc); HRMS (ESI): m/z: calcd for $C_{38}H_{54}NaO_3Si$: 609.3740 $[M+Na]^+$; found: 609.3746.

3.1.10. Acetic acid [(4*R*,4a*R*,6*R*,11*R*,12a*R*)-11-(*tert*-butyl-diphenyl-silanyloxy)-4-isopropyl-1-methyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (14). Compound **12** (67 mg, 0.12 mmol) was dissolved in degassed CH_2Cl_2 (12 mL). Second generation RCM catalyst **13** (5 mg, 6 μmol) in degassed CH_2Cl_2 (2 mL) was slowly added. The mixture stirred for 2 days at room temperature. Additional catalyst **13** (2 mg, 2 μmol) in degassed CH_2Cl_2 (1 mL) was slowly added. The mixture stirred for additional 3 days at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 14:1) to recover unreacted **12** (6 mg) and to provide the bicyclic product **14** (57 mg, 88% yield, 95% considering the recovered starting material) as colorless oils. R_f=0.43 (hexane/EtOAc 14:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.72–7.62 (m, 4H), 7.44–7.33 (m, 6H), 5.86 (dt, J=11.1, 4.7 Hz, 1H), 5.51 (ddd, J=11.7, 3.9 Hz, 1H), 5.20 (m, 1H), 5.13 (m, 1H), 4.17 (m, 1H), 2.77–2.49 (m, 2H), 2.29–2.25 (m, 1H), 2.15 (m, 1H), 2.05–0.85 (m, 23H), 0.89–0.85 (m, 1H), 0.81 (d, J=6.6 Hz, 3H), 0.77–0.65 (m, 1H), 0.61 (d, J=6.6 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=170.4, 138.5, 135.7 (4C), 134.4 (2C), 129.5 (2C), 127.5 (4C), 126.9 (2C), 120.4, 72.8 (2C), 37.8, 37.0, 36.6, 34.7, 31.9, 31.6, 26.9 (4C), 26.2, 24.2, 23.9, 21.2, 20.9, 19.2, 14.9; IR (CCl_4): ν=3070, 2958, 2926, 2856, 1740, 1460, 1427, 1368, 1110, 1067; $[\alpha]_D^{20}$=+41.0 (c=1.26, EtOAc); HRMS [EI (70 eV)]: m/z: calcd for $C_{36}H_{50}O_3Si$: 558.3529 $[M]^+$; found: 558.3532.

3.1.11. Acetic acid [(4*R*,4a*R*,6*R*,11*R*,12a*R*)-11-hydroxy-4-isopropyl-1-methyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (15). Compound **14** (19 mg, 0.04 mmol) was dissolved in THF (0.55 mL) and TBAF (0.17 mL, 0.17 mmol, 1.0 M in THF) was added. The reaction mixture was stirred for 16 h at room temperature. EtOAc (10 mL) was added, the organic layer was washed with an aqueous phosphate buffer solution (2×5 mL, pH=7) and then dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 4:1) to yield compound **15** (10 mg, 94%) as a colorless oil. R_f=0.27 (hexane/EtOAc 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=5.72 (dt, J=11.2, 3.9 Hz, 1H), 5.53 (dt, J=11.7, 4.0 Hz, 1H), 5.31–5.12 (m, 2H), 4.26–4.19 (m, 1H), 2.85–2.66 (m, 2H), 2.42–1.16 (m,

19H), 0.85 (d, J=6.8 Hz, 3H), 0.67 (d, J=6.8 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=170.4, 138.4, 127.9, 126.2, 121.1, 72.6, 71.3, 38.0, 37.4, 36.8, 34.7, 31.9, 31.8, 27.0, 26.4, 24.4, 24.3, 21.2, 21.0, 15.1; IR (CCl_4): ν=3634, 3621, 2924, 2843, 1739, 1460, 1382, 1364; $[\alpha]_D^{20}$=+4.6 (c=0.46, EtOAc); HRMS (ESI): m/z: calcd for $C_{20}H_{32}NaO_3$: 343.2249 $[M+Na]^+$; found: 343.2241.

3.1.12. (*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid [(1*R*,4a*R*,6*R*,11*R*,12a*R*)-11-acetoxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (17). Compound **15** (11 mg, 0.04 mmol) was dissolved in CH_2Cl_2 (2 mL) and added to mixed anhydride **16** (prepared according to Ref. 6b; 123 mg, 0.52 mmol). NEt_3 (52 mg, 0.52 mmol) and DMAP (4 mg, 0.04 mmol) were added and the solution stirred for 3 days at room temperature. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 1:4) to recover unreacted **15** (4 mg) and to yield compound **17** (9 mg, 59% yield, 87% considering the recovered starting material) as a colorless oil. R_f=0.25 (hexane/EtOAc 1:4); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.55 (d, J=15.6 Hz, 1H), 7.47 (s, 1H), 7.09 (s, 1H), 6.54 (d, J=15.6 Hz, 1H), 5.74–5.66 (m, 1H), 5.62–5.55 (m, 1H), 5.45–5.39 (m, 1H), 5.34 (br s, 1H), 5.24–5.18 (m, 1H), 3.72 (s, 3H), 2.88–2.77 (m, 2H), 2.40–2.25 (m, 2H), 2.23–2.18 (m, 1H), 2.07 (s, 3H), 2.05–1.26 (m, 12H), 0.87 (d, J=6.7 Hz, 3H), 0.70 (d, J=6.7 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=170.4, 166.7, 137.9, 138.4, 135.9, 127.9, 126.4, 122.2, 121.0, 116.4, 73.6, 72.5, 37.5, 37.3, 34.6, 33.5, 32.7, 31.6, 29.6, 29.2, 26.9, 26.2, 24.3, 24.2, 21.2, 20.9, 15.1; IR (CCl_4): ν=2960, 2850, 1745, 1705, 1640, 1450, 1440, 1380, 1345, 1295, 905; $[\alpha]_D^{20}$=−29.0 (c=0.71, EtOAc); HRMS [EI (30 eV)]: m/z: calcd for $C_{27}H_{38}N_2O_4$: 454.2832 $[M]^+$; found: 454.2802.

3.1.13. (4*R*,4a*R*,6*R*,11*R*,12a*R*)-11-(*tert*-Butyl-diphenyl-silanoxy)-4-isopropyl-1-methyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-ol (18). Compound **14** (30 mg, 0.05 mmol) was dissolved in MeOH (1 mL). K_2CO_3 (17 mg, 0.10 mmol) was added and the solution stirred for 15 h at room temperature. H_2O (2 mL) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3×5 mL), the combined organic extracts were washed with a saturated aqueous NaCl solution (2×5 mL) and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 9:1) to give compound **18** (26 mg, 94%) as a colorless oil. R_f=0.25 (hexane/EtOAc 9:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.74–7.61 (m, 4H), 7.46–7.31 (m, 6H), 5.82 (dt, J=11.3, 5.1 Hz, 1H), 5.52 (dt, J=11.3, 5.1 Hz, 1H), 5.13 (br s, 1H), 4.23–4.04 (m, 2H), 2.70–2.49 (m, 2H), 2.33–2.04 (m, 3H), 1.99–1.18 (m, 13H), 1.08 (s, 9H), 0.84 (d, J=6.8 Hz, 3H), 0.72 (d, J=6.8 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=138.5, 135.7 (4C), 134.5, 134.4, 129.4 (2C), 127.9, 127.5 (4C), 126.6, 120.4, 72.7, 71.0, 37.9, 37.3, 36.6, 35.5, 33.7, 32.0, 29.1, 27.0 (4C), 24.3, 23.9, 21.0, 19.2, 15.3; IR (CCl_4): ν=3611, 2942, 2921, 2842, 1472, 1458, 1427, 1389, 1369, 1109, 1067, 909; $[\alpha]_D^{20}$=+25.3 (c=0.73, EtOAc); HRMS (ESI): m/z: calcd for $C_{34}H_{48}NaO_2Si$: 539.3321 $[M+Na]^+$; found: 539.3306.

3.1.14. (4*R*,4a*R*,11*R*,12a*R*)-11-(*tert*-Butyl-diphenyl-silanoxy)-4-isopropyl-1-methyl-3,4a,5,7,10,11,12,12a-octahydro-4*H*-benzocyclodecen-6-one (19). $(COCl)_2$ (91 mg, 0.72 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and cooled to −60°C. DMSO (77 mg, 0.98 mmol) was added and the solution stirred for 10 min at −60°C. Compound **18** (62 mg, 0.12 mmol) in CH_2Cl_2 (0.5 mL) was added and the solution stirred for further 30 min at −60°C. NEt_3 (199 mg, 1.97 mmol) was added, the solution was allowed to warm to 0°C over 1 h and stirred additional 10 min at 0°C. An aqueous phosphate buffer solution (3 mL, pH=7) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 9:1) to provide unreacted **18** (9 mg) and ketone **19** (50 mg, 81% yield, 95% considering the recovered starting material) as colorless oils. R_f=0.55 (hexane/EtOAc 9:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.77–7.59 (m, 4H), 7.47–7.29 (m, 6H), 6.19–6.06 (m, 1H), 5.97–5.84 (m, 1H), 5.06 (br s, 1H), 3.96–3.82 (m, 1H), 3.20–2.87 (m, 3H), 2.32–1.95 (m, 4H), 1.89–1.61 (m, 5H), 1.41–1.18 (m, 5H), 1.07 (s, 9H), 0.87 (d, J=6.8 Hz, 3H), 0.69 (d, J=6.8 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=213.0, 139.2, 135.8 (4C), 134.0 (2C), 131.4, 129.7, 129.6, 127.6 (2C), 127.5 (2C), 123.7, 116.7, 73.0, 44.1, 38.7, 36.0, 36.7 (2C), 36.5, 32.1, 27.0 (3C), 26.6, 24.1, 22.6, 21.1, 19.2, 14.3; IR (CCl_4): ν=3022, 2955, 2922, 2899, 2860, 1708, 1705, 1469, 1427; $[\alpha]_D^{20}$=+49.0 (c=0.79, EtOAc); HRMS (ESI): m/z: calcd for $C_{34}H_{46}NaO_2Si$: 537.3165 $[M+Na]^+$; found: 537.3139.

3.1.15. (4*R*,4a*R*,11*R*,12a*R*)-11-Hydroxy-4-isopropyl-1-methyl-3,4a,5,7,10,11,12,12a-octahydro-4*H*-benzocyclodecen-6-one (20). Compound **19** (16 mg, 0.03 mmol) was dissolved in THF (0.50 mL) and TBAF (0.06 mL, 0.06 mmol, 1.0 M in THF) was added. The reaction mixture was stirred 23 h at room temperature. Additional TBAF (0.06 mL, 0.06 mmol, 1.0 M in THF) was then added and the solution stirred for further 5 h at room temperature. An aqueous phosphate buffer solution (1.0 mL, pH=7) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3×5 mL) and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 8:2) to yield compound **20** (10 mg, quant.) as a colorless oil. R_f=0.17 (hexane/EtOAc 8:2); ^{1}H NMR (200 MHz, $CDCl_3$): δ=6.01–5.84 (m, 2H), 5.23 (br s, 1H), 4.07–3.93 (m, 1H), 3.24–2.87 (m, 3H), 2.42–2.08 (m, 4H), 1.92–1.01 (m, 11H), 0.87 (d, J=6.9 Hz, 3H), 0.71 (d, J=6.9 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=212.8, 139.0, 130.3, 124.6, 119.5, 71.9, 44.2, 39.0, 38.0, 37.1, 37.0, 36.9, 32.1, 26.6, 24.2, 23.3, 21.2, 14.4; IR (CCl_4): ν=3627, 2960, 2951, 2904, 1709, 1460, 1442, 1389, 1371, 909; $[\alpha]_D^{20}$=−4.7 (c=0.51, EtOAc).

3.1.16. (*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid [(1*R*,4a*R*,6*R*,12a*R*)-1-isopropyl-4-methyl-11-oxo-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-enyl] ester (21). Compound **20** (9 mg, 0.03 mmol) was dissolved in CH_2Cl_2 (2 mL) and added to mixed anhydride

16 (prepared according to Ref. 6b; 110 mg, 0.47 mmol). NEt_3 (48 mg, 0.47 mmol) and DMAP (4 mg, 0.03 mmol) were added and the solution was stirred for 3 days at 40°C. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 1:5) to yield compound **21** (7 mg, 52%) as a colorless oil. R_f=0.18 (hexane/EtOAc 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.55 (d, J=15.6 Hz, 1H), 7.47 (s, 1H), 7.09 (s, 1H), 6.55 (d, J=15.6 Hz, 1H), 5.97–5.88 (m, 2H), 5.26 (br s, 1H), 5.15 (d, J=12.0 Hz, 1H), 3.72 (s, 3H), 3.25–3.15 (m, 1H), 3.09–2.96 (m, 2H), 2.46–2.14 (m, 4H), 1.94–1.55 (m, 7H), 1.48–1.17 (m, 3H), 0.89 (d, J=6.9 Hz, 3H), 0.75 (d, J=6.9 Hz, 3H); ^{13}C NMR (100.8 MHz, $CDCl_3$): δ=212.7, 166.6, 139.1, 139.0. 138.6, 136.0, 130.6, 124.7, 122.3, 119.2, 116.3, 73.7, 44.1, 39.1, 37.0, 36.8 (2C), 34.1, 33.5, 29.7, 26.7, 24.2, 23.1, 21.1, 14.4; IR (CCl_4): ν=2945, 2920, 2890, 1703, 1640, 1452, 1381, 1390, 1153, 1104, 905; $[\alpha]_D^{20}$=−15.6 (c=0.34, EtOAc); HRMS (ESI): m/z: calcd for $C_{25}H_{35}N_2O_3$: 411.2648 $[M+H]^+$; found: 411.2648.

3.1.17. (1*R*,4a*R*,6*R*,12a*R*)-*tert*-Butyl-(1-isopropyl-4-methyl-11-methylene-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yloxy)-diphenyl-silane (22). Ph_3PCH_3Br (17 mg, 0.047 mmol) was dissolved in THF (0.2 mL). *n*-BuLi (13 μL, 0.020 mmol, 1.6 M in *n*-hexane) was added and the solution was stirred for 1 h at room temperature. Compound **19** (8 mg, 0.016 mmol) was added in THF (600 μL) and the solution was heated to 50°C for 12 h. H_2O (2.0 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3×5 mL) and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane) to yield compound **22** (8 mg, 94%) as a colorless oil. R_f=0.32 (hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.72–7.65 (m, 4H), 7.46–7.33 (m, 6H), 6.03–5.87 (m, 1H), 5.73–5.61 (m, 1H), 5.11 (br s, 1H), 4.94 (br s, 1H), 4.75 (br s, 1H), 4.04–3.93 (m, 1H), 3.08 (dd, J=16.1, 5.9 Hz, 1H), 2.84–2.70 (m, 2H), 2.19–1.44 (m, 8H), 1.41–1.17 (m, 6H), 1.09 (s, 9H), 0.88 (d, J=5.8 Hz, 3H), 0.75 (d, J=5.8 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=138.4, 135.9 (4C), 134.5 (2C), 133.8, 129.6, 129.5, 128.8, 128.6 (2C), 127.6, 127.5 (2C), 119.2, 111.1, 73.3, 39.4, 37.7, 37.3, 37.1, 36.3, 32.1, 30.7, 27.1 (3C), 26.6, 24.5, 23.1, 21.1 (2C), 19.3; IR (CCl_4): ν=3070, 3018, 2955, 2925, 2856, 1470, 1459, 1423, 1385, 1366, 1308, 1108, 1071; $[\alpha]_D^{20}$=+68.4 (c=0.25, EtOAc).

3.1.18. (1*R*,4a*R*,6*R*,12a*R*)-1-Isopropyl-4-methyl-11-methylene-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-ol (23). Compound **22** (8 mg, 0.015 mmol) was dissolved in THF (1.0 mL) and TBAF (73 μL, 0.075 mmol, 1.0 M in THF) was added. The reaction mixture was stirred 12 h at room temperature. Additional TBAF (73 μL, 0.075 mmol, 1.0 M in THF) was added and the reaction mixture was stirred for another 12 h at room temperature. An aqueous phosphate buffer solution (1.0 mL, pH=7) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3×5 mL) and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc 9:1) to yield compound **23** (4 mg, quant.) as a colorless oil. R_f=0.28 (hexanes/EtOAc 9:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=5.76–5.62 (m, 2H), 5.26 (br s, 1H), 4.98 (s, 1H), 4.80 (s, 1H), 4.08–3.97 (m, 1H), 3.24–3.12 (m, 1H), 2.98–2.74 (m, 2H), 2.29–1.67 (m, 9H), 1.61–1.34 (m, 5H), 0.87 (d, J=6.7 Hz, 4H), 0.77 (d, J=6.7 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=133.8, 129.8, 127.0, 123.3, 120.0, 111.7, 72.0, 39.7, 37.7, 37.5, 36.9, 36.7, 32.2, 31.1, 26.8, 24.6, 23.6, 21.1 (2C); IR (CCl_4): ν=3632, 3080, 3024, 2967, 2930, 1461, 1455, 1440, 1389, 1370; $[\alpha]_D^{20}$=+36.4 (c=0.17, EtOAc).

3.1.19. (*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid [(1*R*,4a*R*,6*R*,12a*R*)-(1-isopropyl-4-methyl-11-methylene-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (24). Compound **23** (4 mg, 0.0091 mmol) was dissolved in CH_2Cl_2 (1.0 mL) and added to mixed anhydride **16** (prepared according to Ref. 6b; 51 mg, 0.137 mmol). NEt_3 (22 mg, 0.219 mmol) and DMAP (1 mg, 0.008 mmol) were added and the solution was stirred for 3 days at room temperature. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 1:4) to yield compound **24** (3 mg, 47%) as a colorless oil. R_f=0.30 (hexane/EtOAc 1:4); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.62 (br s, 1H), 7.54 (d, J=15.7 Hz, 1H), 7.08 (br s, 1H), 6.59 (d, J=15.7 Hz, 1H), 5.74–5.62 (m, 2H), 5.30–5.11 (m, 2H), 5.04 (br s, 1H), 4.72 (br s, 1H), 3.73 (s, 3H), 3.25–2.73 (m, 3H), 2.34–1.55 (m, 7H), 1.44–1.21 (m, 6H), 0.87 (d, J=6.7 Hz, 4H), 0.77 (d, J=6.7 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=164.3, 148.2, 138.2, 135.4, 131.5, 131.3, 129.6, 127.6, 119.7, 113.8, 111.6, 74.7, 39.3, 37.4, 36.9, 36.2, 34.8, 33.7, 30.9, 29.7, 29.5, 26.5, 24.5, 23.4, 21.0 (2C); IR (CCl_4): ν=3380, 3075, 2956, 2922, 2856, 1766, 1709, 1645, 1460, 1428, 1382, 1368, 1305, 1159, 1099; $[\alpha]_D^{20}$=+6.0 (c=0.05, EtOAc); HRMS (ESI): m/z: calcd for $C_{26}H_{37}N_2O_2$: 409.2855 $[M+H]^+$; found: 409.2855.

3.1.20. (2*S*,3*S*)-1-{(1*R*,2*R*,6*R*)-2-[(2*R*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enyl}-3-methoxymethoxy-pent-4-en-2-ol (25) and (2*R*,3*R*)-1-{(1*R*,2*R*,6*R*)-2-[(2*R*)-2-(*tert*-butyl-diphenyl-silanyloxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enyl}-3-methoxymethoxy-pent-4-en-2-ol (26). Methoxymethyl allyl ether (180 mg, 1.75 mmol) in THF (4.0 mL) was cooled to −78°C and *sec*-BuLi (1.10 mL, 1.45 mmol, 1.3 M in cyclohexane) was added. The reaction solution was stirred at −78°C for 30 min and ^{1}Ipc$_2$BOMe (1.60 mL, 1.45 mmol, 0.93 M in THF) was then added. Stirring was maintained for 1 h, $BF_3{\cdot}Et_2O$ (263 mg, 1.86 mmol) was then added, followed by aldehyde **10** (293 mg, 0.58 mmol) in THF (2.0 mL). The mixture was stirred at −78°C for 5 h and then slowly warmed to room temperature. An aqueous NaOH solution (4.0 mL, 6.0 M) and H_2O_2 (4.0 mL, 35%) were then added and the mixture was left stirring overnight. H_2O (5 mL) was added and the aqueous layer was extracted with EtOAc (3×10 mL) and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 6:1) to provide unreacted **10** (56 mg), **25** (246 mg, 70%) and **26** (25 mg, 7%) as colorless oils (total yield=77%, 84% considering the recovered starting

material, de=82%, **25/26** 10:1). **25**: R_f=0.43 (hexane/EtOAc 6:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.95–7.66 (m, 4H), 7.45–7.30 (m, 6H), 5.91–5.51 (m, 2H), 5.32–5.16 (m, 3H), 5.01–4.90 (m, 2H), 4.72 (d, J=6.7 Hz, 1H), 4.56 (d, J=6.7 Hz, 1H), 3.95 (q, J=5.9 Hz, 1H), 3.79–3.72 (m, 1H), 3.58–3.47 (m, 1H), 3.38 (s, 3H), 2.35–2.14 (m, 5H), 1.93–1.14 (m, 11H), 1.05 (s, 9H), 0.79 (d, J=6.6 Hz, 3H), 0.77 (d, J=6.6 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=136.4, 135.9 (4C), 135.1, 134.9, 134.7, 134.6, 129.4 (2C), 127.4 (4C), 120.9, 119.9, 117.0, 93.9, 81.9, 72.2, 71.4, 55.7, 41.3, 39.3, 37.1, 35.8, 34.3, 31.3, 27.5, 27.1 (3C), 23.9, 22.9, 21.2, 19.3, 19.2; IR (CCl_4): ν=3590, 3078, 2955, 2893, 2860, 1473, 1462, 1430, 1390, 1369, 1152, 1108, 935, 915; $[\alpha]_D^{20}$=+43.8 (c=0.90, EtOAc); HRMS (ESI): m/z: calcd for $C_{38}H_{56}NaO_4Si$: 627.3845 $[M+Na]^+$; found: 627.3828; **26**: R_f=0.37 (hexane/EtOAc 6:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.71–7.60 (m, 4H), 7.47–7.30 (m, 6H), 5.96–5.77 (m, 1H), 5.65–5.49 (m, 1H), 5.38–5.21 (m, 2H), 5.16 (br s, 1H), 5.07–4.92 (m, 2H), 4.73 (d, J=6.7 Hz, 1H), 4.58 (d, J=6.7 Hz, 1H), 3.98–3.83 (m, 1H), 3.81–3.69 (m, 1H), 3.65–3.50 (m, 1H), 3.39 (s, 3H), 2.46–1.95 (m, 4H), 1.90–0.98 (m, 20H), 0.90–0.87 (m, 1H), 0.83 (d, J=6.8 Hz, 3H), 0.69 (d, J=6.8 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=137.3, 135.9 (4C), 135.1, 134.8, 134.7 (2C), 129.4 (2C), 127.4 (4C), 121.9, 120.2, 117.0, 93.7, 82.4, 72.1, 70.3, 55.8, 40.8, 37.5, 37.1, 35.8, 35.4, 31.3, 29.7, 27.0 (3C), 26.8, 24.3, 23.9, 21.1, 19.3; IR (CCl_4): ν=3600, 3080, 2960, 2938, 2899, 2862, 1475, 1432, 1391, 1372, 1158, 1108, 912; $[\alpha]_D^{20}$=+48.1 (c=1.09, EtOAc); HRMS (ESI): m/z: calcd for $C_{38}H_{56}NaO_4Si$: 627.3846 $[M+Na]^+$; found: 627.3860.

3.1.21. 2,2-Dimethyl-propionic acid {(1*S*,2*S*)-1-{(1*R*,2*R*,6*R*)-2-[(2*R*)-2-(*tert*-butyl-diphenyl-silanyloxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enylmethyl}-2-methoxymethoxy-but-3-enyl} ester (27). Compound **25** (173 mg, 0.29 mmol) was dissolved in pyridine (2.0 mL). DMAP (4 mg, 0.03 mmol) and PivCl (172 mg, 1.43 mmol) were added and the mixture was stirred at room temperature for 72 h. EtOAc (10 mL) was added, the organic layer was washed with a saturated aqueous $KHSO_4$ solution (2×10 mL), the combined aqueous layers were back extracted with EtOAc (3×10 mL) and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 9:1) to give compound **27** (158 mg, 80%) as a colorless oil. R_f=0.52 (hexane/EtOAc 9:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.71–7.66 (m, 4H), 7.45–7.28 (m, 6H), 5.85–5.59 (m, 2H), 5.29–5.17 (m, 3H), 5.03–4.90 (m, 3H), 4.65 (d, J= 6.3 Hz, 1H), 4.56 (d, J=6.3 Hz, 1H), 4.09–3.87 (m, 2H), 3.35 (s, 3H), 2.30–2.12 (m, 3H), 1.85 (br s, 1H), 1.72–1.22 (m, 11H), 1.18 (s, 9H), 1.04 (s, 9H), 0.82 (d, J=6.3 Hz, 3H), 0.72 (d, J=6.3 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=177.6, 135.9 (4C), 135.3, 134.8, 134.6 (2C), 134.1, 129.5 (2C), 127.5 (4C), 121.0, 119.0, 117.2, 94.4, 77.8, 72.2, 71.7, 55.6, 41.4, 39.4, 36.8, 34.8, 32.7, 27.4, 27.3 (3C), 27.2, 27.0 (3C), 23.6, 22.5, 21.0, 20.6, 19.3 (2C); IR (CCl_4): ν=3061, 2942, 2920, 2882, 2842, 1722, 1455, 1467, 1458, 1423, 1392, 1385, 1362, 1150, 1107, 1098, 909; $[\alpha]_D^{20}$=+25.5 (c=0.78, EtOAc); HRMS (ESI): m/z: calcd for $C_{43}H_{64}NaO_5Si$: 711.4420 $[M+Na]^+$; found: 711.4412.

3.1.22. 2,2-Dimethyl-propionic acid {(1*S*,2*S*)-1-{(1*R*,2*R*,6*R*)-2-[(2*R*)-2-(*tert*-butyl-diphenyl-silanoxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enylmethyl}-2-hydroxy-but-3-enyl} ester (28). Compound **27** (10 mg, 0.015 mmol) was dissolved in CH_2Cl_2 (0.3 mL) and cooled to −78°C. PhSH (2 mg, 0.015 mmol) and $BF_3{\cdot}Et_2O$ (4 mg, 0.029 mmol) were added and the solution was allowed to warm to −10°C and stirred at −10°C for 2 h. Then a saturated aqueous $NaHCO_3$ solution (2 mL) was added and the solution was warmed up to room temperature. The layers were separated, the aqueous layer was extracted with EtOAc (3×5 mL) and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 8:2) to give compound **28** (6 mg, 64%) as a colorless oil. R_f=0.54 (hexane/EtOAc 8:2); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.71–7.67 (m, 4H), 7.41–7.31 (m, 6H), 5.89–5.72 (m, 2H), 5.34 (br s, 1H), 5.25–5.14 (m, 2H), 5.03–4.91 (m, 3H), 4.08 (br s, 1H), 3.93–3.87 (m, 1H), 2.27–2.16 (m, 3H), 2.01–1.22 (m, 14H), 1.18 (s, 9H), 1.04 (s, 9H), 0.93–0.88 (m, 1H), 0.82 (d, J=6.4 Hz, 3H), 0.72 (d, J=6.4 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=176.1, 137.1 (2C), 136.4, 135.9 (2C), 135.0 (2C), 134.7, 129.5 (2C), 127.4 (4C), 121.0, 117.2, 116.4, 74.4, 73.4, 72.3, 41.4, 39.2, 36.7, 35.0, 33.3, 28.0, 27.5, 27.3 (3C), 27.0 (3C), 23.8, 22.6, 20.9 (2C), 20.0, 19.3 (2C); IR (CCl_4): ν=3618, 3582, 3060, 2942, 2918, 2842, 1724, 1472, 1465, 1458, 1421, 1382, 1363, 1149, 1101, 1060, 908; $[\alpha]_D^{20}$=+6.1 (c=0.56, EtOAc); HRMS (ESI): m/z: calcd for $C_{41}H_{62}NaO_4Si$: 669.4315 $[M+Na]^+$; found: 669.4299.

3.1.23. 2,2-Dimethyl-propionic acid [(4*R*,4a*R*,6*S*,7*S*,11*R*,12a*R*)-11-(*tert*-butyl-diphenyl-silanoxy)-7-hydroxy-4-isopropyl-1-methyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (29). Compound **28** (33 mg, 0.05 mmol) was dissolved in degassed CH_2Cl_2 (5.1 mL). Second generation RCM catalyst **13** (2 mg, 2.5 μmol) in degassed CH_2Cl_2 (0.5 mL) was slowly added. The reaction mixture was stirred for 2 days at room temperature. Additional catalyst **13** (1 mg, 1.3 μmol) in degassed CH_2Cl_2 (0.2 mL) was slowly added and the mixture stirred for further 2 days at room temperature. Additional catalyst **13** (1 mg, 1.3 μmol) in degassed CH_2Cl_2 (0.2 mL) was slowly added and the mixture stirred for further 1 day at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 8:2) to give compound **29** (23 mg, 73%) as a colorless oil. R_f=0.44 (hexane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.73–7.65 (m, 4H), 7.47–7.35 (m, 6H), 5.99 (dt, J=11.5, 5.2 Hz, 1H), 5.58 (t, J=10.5 Hz, 1H), 5.14 (br s, 1H), 5.05–4.96 (m, 1H), 4.77 (t, J=9.9 Hz, 1H), 4.23–4.16 (m, 1H), 2.65–2.57 (m, 1H), 2.32–2.27 (m, 1H), 1.89–1.54 (m, 9H), 1.40–1.05 (m, 23H), 0.84 (d, J=6.8 Hz, 3H), 0.64 (d, J=6.8 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=178.1, 137.1, 135.8 (4C), 135.4, 134.8, 134.5 (2C), 129.4 (2C), 127.4 (4C), 121.0, 117.2, 116.4, 74.4, 73.3, 72.2, 41.3, 39.2, 36.6, 34.6, 33.1, 27.7, 27.3 (3C), 26.9 (3C), 23.6, 22.6, 20.9 (2C), 20.0; IR (CCl_4): ν=3630, 2958, 2925, 2852, 1730, 1425, 1367, 1155, 1112, 908; $[\alpha]_D^{20}$=+17.5 (c=0.60, EtOAc); HRMS (ESI): m/z: calcd for $C_{39}H_{56}NaO_4Si$: 639.3846 $[M+Na]^+$; found: 639.3855.

3.1.24. 2,2-Dimethyl-propionic acid [(4*R*,4a*R*,6*S*,7*S*,11-*R*,12a*R*)-11-(*tert*-butyl-diphenyl-silanyloxy)-4-isopropyl-7-methoxy-1-methyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (30). Compound **29** (14 mg, 0.023 mmol) was dissolved in CH_2Cl_2 (0.2 mL). 2,6-Di-*tert*-butyl-pyridine (44 mg, 0.23 mmol) and MeOTf (19 mg, 0.12 mmol) were added and the solution stirred for 18 h at 40°C. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 9:1) to give compound **30** (14 mg, 96%) as a colorless oil. R_f=0.28 (hexane/EtOAc 9:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.74–7.60 (m, 4H), 7.54–7.27 (m, 6H), 6.08 (dt, J=11.4, 5.3 Hz, 1H), 5.40 (t, J=10.7 Hz, 1H), 5.16–5.01 (m, 2H), 4.29–4.08 (m, 2H), 3.18 (s, 3H), 2.68–2.49 (m, 1H), 2.35–2.17 (m, 1H), 2.09–0.84 (m, 31H), 0.80 (d, J=6.8 Hz, 3H), 0.57 (d, J=6.8 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=177.7, 138.6, 135.8 (4C), 134.3 (2C), 130.9, 129.6 (2C), 129.2, 127.6 (4C), 120.5, 78.8, 74.8, 72.2, 56.2, 37.6, 37.1, 36.4, 35.3, 32.6, 29.7, 27.2 (3C), 27.0 (3C), 26.9, 26.7, 24.3, 24.1, 21.0 (2C), 19.2; IR (CCl_4): ν=2948, 2920, 2848, 1723, 1475, 1422, 1385, 1363, 1279, 1155, 1099, 1059; $[\alpha]_D^{20}$=+7.8 (c=0.77, EtOAc); HRMS (ESI): m/z: calcd for $C_{40}H_{58}NaO_4Si$: 653.4002 $[M+Na]^+$; found: 653.3986.

3.1.25. 2,2-Dimethyl-propionic acid [(4*R*,4a*R*,6*S*,7*S*,11-*R*,12a*R*)-11-hydroxy-4-isopropyl-7-methoxy-1-methyl-3,4,4a,5,6,7, 10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (31). Compound **30** (14 mg, 0.022 mmol) was dissolved in THF (0.50 mL) and TBAF (0.044 mL, 0.044 mmol, 1.0 M in THF) was added. The reaction mixture was stirred 14 h at room temperature. An aqueous phosphate buffer solution (1.0 mL, pH=7) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3×5 mL) and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc 8:2) to yield compound **31** (8 mg, 89%) as a colorless oil. R_f=0.11 (hexanes/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.87 (dt, J=11.6, 5.4 Hz, 1H), 5.44 (t, J=10.8 Hz, 1H), 5.32 (br s, 1H), 5.12–5.08 (m, 1H), 4.34–4.23 (m, 2H), 3.26 (s, 3H), 2.80–2.74 (m, 1H), 2.48–2.2.31 (m, 1H), 2.25–1.12 (m, 20H), 1.05–0.89 (m, 3H), 0.86 (d, J=6.8 Hz, 3H), 0.64 (d, J=6.8 Hz, 3H); ^{13}C NMR (100.8 MHz, $CDCl_3$): δ=177.6, 137.5, 130.0, 129.5, 121.0, 78.3, 74.7, 70.7, 56.2, 37.8, 37.3, 36.9, 36.6, 35.3, 32.4, 29.6, 27.2 (3C), 26.9, 26.7, 24.4, 21.0 (2C); IR (CCl_4): ν=3620, 2954, 2923, 2864, 1728, 1478, 1451, 1395, 1386, 1367, 1280, 1160, 1099, 905; $[\alpha]_D^{20}$=−8.4 (c=0.37, EtOAc).

3.1.26. (*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid [(1*R*,4a*R*,6*R*,10*S*,11*S*,12a*R*)-11-(2,2-dimethyl-propionyl-oxy)-1-isopropyl-10-methoxy-4-methyl-1,2,4a,5,6,7, 10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (32). Compound **31** (6 mg, 0.0153 mmol) was dissolved in CH_2Cl_2 (1.8 mL) and added to mixed anhydride **16** (prepared according to Ref. 6b; 76 mg, 0.325 mmol). NEt_3 (33 mg, 0.325 mmol) and DMAP (2 mg, 0.0153 mmol) were added and the solution stirred for 15 days at room temperature. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 1:5) to yield compound **32** (6 mg, 66%) as a colorless oil. R_f=0.22 (hexane/EtOAc 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.56 (d, J=15.6 Hz, 1H), 7.48 (s, 1H), 7.10 (s, 1H), 6.53 (d, J=15.6 Hz, 1H), 5.96–5.89 (m, 1H), 5.52–5.38 (m, 2H), 5.32 (br s, 1H), 5.12 (d, J=7.3 Hz, 1H), 4.27 (t, J=9.9 Hz, 1H), 3.73 (s, 3H), 3.26 (s, 3H), 2.88–2.76 (m, 1H), 2.54–2.46 (m, 1H), 2.13–1.14 (m, 24H), 0.99–0.87 (m, 2H), 0.85 (d, J=5.1 Hz, 3H), 0.65 (d, J=5.1 Hz, 3H); ^{13}C NMR (100.8 MHz, $CDCl_3$): δ=177.7, 166.6, 139.2, 138.5, 136.1, 135.7, 130.3, 129.6, 122.3, 121.1, 116.3, 79.7, 74.7, 72.9, 56.7, 37.4 (2C), 35.3, 33.5, 33.2, 30.7, 29.6, 29.3, 27.2 (3C), 26.9, 26.6, 24.3, 24.4, 21.0 (2C); IR (CCl_4): ν=2960, 2931, 2889, 2861, 1731, 1712, 1645, 1481, 1460, 1389, 1300, 1157, 1103; $[\alpha]_D^{20}$=−17.0 (c=0.33, EtOAc); HRMS (ESI): m/z: calcd for $C_{32}H_{50}NaN_2O_5$: 565.3617 $[M+Na]^+$; found: 565.3611.

3.1.27. 2,2-Dimethyl-propionic acid [(4*R*,4a*R*,6*S*,7*S*,11-*R*,12a*R*)-7-acetoxy-11-(*tert*-butyl-diphenyl-silanyloxy)-4-isopropyl-1-methyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (33). Compound **29** (16 mg, 0.026 mmol) was dissolved in pyridine (0.5 mL). Ac_2O (5 mg, 0.052 mmol) and DMAP (cat.) were added and the reaction mixture was stirred for 24 h at room temperature. EtOAc (5 mL) was added and the organic layer was washed with a saturated aqueous $KHSO_4$ solution (2×5 mL), the aqueous layer was back extracted with EtOAc (3×5 mL) and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 9:1) to give compound **33** (12 mg, 71%) as a colorless oil. R_f=0.69 (hexane/EtOAc 9:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.69–7.61 (m, 4H), 7.46–7.30 (m, 6H), 6.11–5.87 (m, 2H), 5.45 (t, J=10.7 Hz, 1H), 5.22–5.10 (m, 2H), 4.24–4.18 (m, 1H), 2.88–2.74 (m, 1H), 2.32–2.25 (m, 1H), 2.12–1.95 (m, 4H), 1.84–0.89 (m, 30H), 0.82 (d, J=6.9 Hz, 3H), 0.57 (d, J=6.9 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=177.5, 170.0, 138.8, 135.7 (4C), 134.1 (2C), 132.1, 129.6, 129.5, 127.6 (2C), 127.5 (2C), 126.5, 120.3, 73.6, 72.0, 71.5, 37.7, 37.3, 36.4, 35.3, 32.9, 29.6, 27.0 (7C), 26.5, 24.3, 24.0 (2C), 21.0, 19.2, 14.5; IR (CCl_4): ν=3078, 2959, 2938, 2860, 1739, 1732, 1482, 1460, 1430, 1371, 1155, 1112, 1070; $[\alpha]_D^{20}$=+0.6 (c=0.51, EtOAc); HRMS (ESI): m/z: calcd for $C_{41}H_{58}NaO_5Si$: 681.3951 $[M+Na]^+$; found: 681.3967.

3.1.28. 2,2-Dimethyl-propionic acid [(4*R*,4a*R*,6*S*,7*S*,11-*R*,12a*R*)-7-acetoxy-11-hydroxy-4-isopropyl-1-methyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (34). Compound **33** (11 mg, 0.0167 mmol) was dissolved in THF (0.30 mL) and TBAF (0.033 mL, 0.0334 mmol, 1.0 M in THF) was added. The reaction mixture was stirred 20 h at room temperature. An aqueous phosphate buffer solution (1.0 mL, pH=7) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3×5 mL) and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc 8:2) to yield compound **34** (7 mg, 92%) as a colorless oil. R_f=0.15 (hexanes/EtOAc 8:2); ^{1}H NMR (200 MHz, $CDCl_3$): δ=6.01 (t, J=10.3 Hz, 1H), 5.91 (dt, J=11.4, 5.4 Hz, 1H), 5.47 (t, J=10.7 Hz, 1H), 5.29 (br s, 1H), 5.19 (dd, J=10.1, 6.9 Hz, 1H), 4.46–4.24 (m, 1H), 3.08–2.91 (m, 1H), 2.44–2.33 (m, 1H), 2.18–1.22

(m, 17H), 1.18 (s, 9H), 0.84 (d, J=6.8 Hz, 3H), 0.61 (d, J=6.8 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=177.4, 171.1, 138.8, 130.9, 127.3, 120.9, 73.5, 71.3, 70.5, 37.9, 37.4, 36.6, 35.3, 32.7, 29.7, 27.1 (3C), 26.9, 26.4, 24.4, 21.0 (2C), 14.5; IR (CCl_4): ν=3622, 2957, 2935, 2870, 1745, 1730, 1479, 1452, 1395, 1388, 1369, 1280, 1155; $[\alpha]_D^{20}$=−33.5 (c=0.39, EtOAc); HRMS (ESI): m/z: calcd for $C_{25}H_{40}NaO_5$: 443.2773 $[M+Na]^+$; found: 443.2761.

3.1.29. (*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid [(1*R*,4a*R*,6*R*,10*S*,11*S*,12a*R*)-10-acetoxy-11-(2,2-dimethyl-propionyloxy)-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (35). Compound **34** (6 mg, 0.014 mmol) was dissolved in CH_2Cl_2 (1.6 mL) and added to mixed anhydride **16** (prepared according to Ref. 6b; 50 mg, 0.21 mmol). NEt_3 (21 mg, 0.21 mmol) and DMAP (2 mg, 0.014 mmol) were added and the solution was stirred for 2 days at room temperature. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 1:4) to yield compound **35** (6 mg, 80%) as a colorless oil. R_f=0.20 (hexane/EtOAc 1:4); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.60 (s, 1H), 7.54 (d, J=15.7 Hz, 1H), 7.11 (s, 1H), 6.59 (d, J=15.7 Hz, 1H), 6.04 (t, J=10.4 Hz, 1H), 5.89 (dt, J=11.6, 5.6 Hz, 1H), 5.55–5.45 (m, 2H), 5.32 (s, 1H), 5.23 (dd, J=10.1, 6.8 Hz, 1H), 3.75 (s, 3H), 3.13–3.03 (m, 1H), 2.54–2.48 (m, 1H), 2.22–1.17 (m, 25H), 0.85 (d, J=6.9 Hz, 3H), 0.63 (d, J=6.9 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=177.6, 170.1, 166.7, 138.6, 138.4, 136.1, 130.9, 127.5 (2C), 122.3, 120.9, 116.3, 73.4, 72.8, 71.1, 37.5, 36.5, 35.3, 33.7, 33.5, 30.0, 29.7, 27.2 (3C), 26.8, 26.3, 24.5, 21.0 (3C), 14.5; IR (CCl_4): ν=2961, 2935, 1742, 1733, 1712, 1648, 1390, 1371, 1155; $[\alpha]_D^{20}$=−39.6 (c=0.24, EtOAc); HRMS (ESI): m/z: calcd for $C_{32}H_{47}N_2O_6$: 555.3434 $[M+H]^+$; found: 555.3425.

3.1.30. 2,2-Dimethyl-propionic acid {(4*R*,4a*R*,6*S*,7*S*,11-*R*,12a*R*)-11-(*tert*-butyl-diphenyl-silanyloxy)-4-isopropyl-1-methyl-7-[(2′*)-tetrahydro-pyran-2′-yloxy)]-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl} ester (36). Compound **29** (29 mg, 0.047 mmol) was dissolved in CH_2Cl_2 (0.4 mL). Dihydropyran (6 mg, 0.071 mmol) and PPTS (1 mg, 0.005 mmol) were added and the solution was stirred for 11 h at room temperature. i-Pr_2O (5 mL) was added, the organic layer was washed with a semisaturated NaCl solution (2×5 mL) and the organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 14:1) to yield compound **36** (25 mg, 77%) as a colorless oil. R_f=0.33 (hexane/EtOAc 14:1); ^{1}H NMR (200 MHz, $CDCl_3$, signal doubling due to diastereomers): δ=7.68–7.61 (m, 4H), 7.38–7.28 (m, 6H), 6.08+5.93 (dt, J=11.6, 5.5 Hz, 1H), 5.59+5.32 (t, J=10.4 Hz, 1H), 5.18–5.01 (m, 2H), 4.88–4.61 (m, 2H), 4.23–4.10 (m, 1H), 3.94–3.72 (m, 1H), 3.51–3.33 (m, 1H), 2.76–2.57 (m, 1H), 2.35–2.17 (m, 1H), 2.13–1.95 (m, 1H), 1.91–0.95 (m, 36H), 0.80 (d, J=5.8 Hz, 3H), 0.61–0.55 (m, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$, signal doubling due to diastereomers): δ=177.6+177.4, 138.9+138.8, 135.7 (4C), 134.4+134.2 (2C), 132.0, 130.0+129.5 (2C), 128.4, 127.9+127.5+127.4 (4C), 120.2, 99.2+93.0, 76.5, 74.9+74.6, 72.1+70.5, 61.5+60.4, 37.7, 37.3, 36.5, 35.4, 32.6, 30.4+30.1, 29.6, 27.3 (3C), 27.0+26.6 (3C), 26.3, 25.4, 24.3, 23.9, 21.0 (2C), 19.2, 16.7+16.3, 14.6; IR (CCl_4): ν=3062, 2945, 2918, 2844, 1722, 1474, 1465, 1448, 1422, 1381, 1362, 1151, 1107, 1059, 902; $[\alpha]_D^{20}$=−7.2 (c=1.16, EtOAc); HRMS (ESI): m/z: calcd for $C_{44}H_{64}NaO_5Si$: 723.4421 $[M+Na]^+$; found: 723.4416.

3.1.31. 2,2-Dimethyl-propionic acid {(4*R*,4a*R*,6*S*,7*S*,11*R*,12a*R*)-11-hydroxy-4-isopropyl-1-methyl-[(2′*)-7-(tetrahydro-pyran-2′-yloxy)]-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl} ester (37). Compound **36** (23 mg, 0.033 mmol) was dissolved in THF (2.0 mL) and TBAF (165 μL, 0.165 mmol, 1.0 M in THF) was added. The reaction mixture was stirred 20 h at room temperature. An aqueous phosphate buffer solution (1.0 mL, pH=7) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic extracts were dried over Na_2SO_4 and, after filtration, the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc 4:1) to yield compound **37** (15 mg, quant.) as a colorless oil. R_f=0.10 (hexanes/EtOAc 4:1); ^{1}H NMR (200 MHz, $CDCl_3$, signal doubling due to diastereomers): δ=5.97+5.78 (dt, J=9.3, 5.8 Hz, 1H), 5.60+5.35 (t, J=10.3 Hz, 1H), 5.29–5.01 (m, 2H), 4.93–4.65 (m, 2H), 4.39–4.15 (m, 1H), 4.02–3.73 (m, 1H), 3.55–3.33 (m, 1H), 2.93–2.71 (m, 1H), 2.40–2.22 (m, 1H), 2.17–1.09 (m, 29H), 0.82 (d, J=6.7 Hz, 3H), 0.62+0.59 (d, J=6.7 Hz, 3H); ^{13}C NMR (100.8 MHz, $CDCl_3$, signal doubling due to diastereomers): δ=177.5, 133.8, 129.2, 126.6, 120.9+120.8, 99.3+93.1, 76.5, 74.9+74.7, 70.7+70.4, 61.5+60.6, 37.9+37.8, 37.4, 36.6, 35.5, 32.4, 30.4+30.2, 27.4, 27.3 (3C), 27.2, 26.9, 26.7+26.3, 25.5+25.4, 24.5, 21.1 (2C), 18.7+18.4; IR (CCl_4): ν=3620, 3440, 2950, 2865, 1723, 1477, 1451, 1392, 1385, 1365, 1279, 1155, 1110, 1072, 1050, 905; $[\alpha]_D^{20}$=−36.1 (c=0.75, EtOAc); HRMS (ESI): m/z: calcd for $C_{28}H_{46}NaO_5$: 485.3243 $[M+Na]^+$; found: 485.3238.

3.1.32. 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid {(1*R*,4a*R*,6*R*,10*S*,11*S*,12a*R*)-11-(2,2-dimethyl-propionyloxy)-1-isopropyl-4-methyl-10-[(2′*)-(tetrahydro-pyran-2-yloxy)]-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl} ester (38). Compound **37** (15 mg, 0.032 mmol) was dissolved in CH_2Cl_2 (2.0 mL) and added to mixed anhydride **16** (prepared according to Ref. 6b; 118 mg, 0.494 mmol). NEt_3 (50 mg, 0.494 mmol) and DMAP (4 mg, 0.032 mmol) were added and the solution was stirred for 3 days at room temperature. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 1:4) to yield compound **38** (12 mg, 61%) as a colorless oil. R_f=0.15 (hexane/EtOAc 1:4); ^{1}H NMR (400 MHz, $CDCl_3$, signal doubling due to diastereomers): δ=7.62 (s, 1H), 7.57+7.53 (d, J=15.7 Hz, 1H), 7.10 (s, 1H), 6.56 (d, J=15.7 Hz, 1H), 5.94+5.75 (dt, J=9.1, 6.2 Hz, 1H), 5.65 (t, J=10.4 Hz, 1H), 5.45–5.37 (m, 2H), 5.30 (s, 1H), 5.23–5.08 (m, 1H), 4.92+4.78 (t, J=10.2 Hz, 1H), 4.90–4.85+4.68–4.65 (m, 1H), 3.99–3.92+3.84–3.77 (m, 1H), 3.74 (s, 3H), 3.57–3.47+3.45–3.38 (m, 1H), 2.97–2.83 (m, 1H), 2.48–2.41 (m, 1H), 2.17–1.38 (m, 15H), 1.33–1.18 (m, 12H), 0.84 (d, J=6.8 Hz, 3H), 0.67–0.61 (m, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$, signal doubling due to diastereomers): δ=177.2, 166.5, 137.9, 135.2, 130.9+130.8, 129.4, 126.7, 122.1, 120.8, 117.0, 99.3+93.3, 74.7+74.5,

73.1, 70.2, 61.5+60.8, 37.4, 36.6, 35.4, 33.7, 30.3, 29.6, 27.3 (3C), 27.0, 26.8, 26.5, 26.2, 25.4, 24.5, 24.3, 21.0 (2C), 19.0+18.7, 14.6; IR (CCl_4): ν=2959, 2877, 1725, 1709, 1645, 1481, 1452, 1385, 1398, 1156, 1113, 909; $[\alpha]_D^{20}$=−44.4 (c=0.59, EtOAc); HRMS (ESI): m/z: calcd for $C_{32}H_{53}N_2O_6$: 597.3904 $[M+H]^+$; found: 597.3900.

3.1.33. 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid [(1*R*,4a*R*,6*R*,10*S*,11*S*,12a*R*)-11-(2,2-dimethyl-propionyl oxy)-10-hydroxy-1-isopropyl-4-methyl-1,2,4a,5,6,7, 10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (39). Compound **38** (13 mg, 0.022 mmol) was dissolved in EtOH (2.0 mL, 80%). PTSA (0.8 mg, 0.0044 mmol) was added and the solution was stirred for 72 h at room temperature. EtOAc (5 mL) was added, the organic layer was washed with a saturated aqueous $NaHCO_3$ solution (2×5 mL), with a saturated aqueous NaCl solution (5 mL) and then the organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (EtOAc) to yield compound **39** (7 mg, 82%) as a colorless oil. R_f=0.16 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.67 (s, 1H), 7.54 (d, J=5.2 Hz, 1H), 7.09 (s, 1H), 6.58 (d, J=5.2 Hz, 1H), 5.77 (dt, J=11.5, 5.3 Hz, 1H), 5.60 (t, J=10.5 Hz, 1H), 5.43–5.37 (m, 1H), 5.29 (s, 1H), 5.11–5.00 (m, 1H), 4.84 (t, J=9.8 Hz, 1H), 3.74 (s, 3H), 2.87–2.78 (m, 1H), 2.51–1.71 (m, 11H), 1.62–1.36 (m, 3H), 1.35–1.15 (m, 10H), 0.84 (d, J=6.8 Hz, 3H), 0.64 (d, J=6.8 Hz, 3H); ^{13}C NMR (100.8 MHz, $CDCl_3$): δ=178.5, 166.5, 138.9, 137.7, 135.1, 131.4, 128.2, 122.4, 121.1, 117.2, 77.7, 73.1, 70.4, 69.5, 37.4, 33.9, 33.1, 30.1, 29.7, 27.3 (3C), 27.2, 26.9, 26.8, 24.4, 24.3, 21.0 (2C), 19.1; IR (CCl_4): ν=3620, 3240, 2957, 2922, 2865, 1709, 1643, 1478, 1455, 1385, 1367, 1322, 1297, 1155, 1109, 1043, 908; $[\alpha]_D^{20}$=−45.0 (c=0.28, EtOAc); HRMS (ESI): m/z: calcd for $C_{30}H_{45}N_2O_5$: 513.3329 $[M+H]^+$; found: 513.3321.

3.1.34. (2*R*,3*R*)-1-{(1*R*,2*R*,6*R*)-2-[(2*R*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enyl}-3-methoxymethoxy-pent-4-en-2-ol (26). Methoxymethyl allyl ether (136 mg, 1.33 mmol) in THF (2.7 mL) was cooled to −78°C and *sec*-BuLi (854 μL, 1.11 mmol, 1.3 M in cyclohexane) was added. The reaction solution was stirred at −78°C for 30 min and ^{d}Ipc$_2$BOMe (1.11 mL, 1.11 mmol, 1.0 M in THF) was then added. Stirring was maintained for 1 h, $BF_3{\cdot}Et_2O$ (213 mg, 1.50 mmol) was then added, followed by aldehyde **10** (279 mg, 0.55 mmol) in THF (3.9 mL). The mixture was stirred at −78°C for 14 h and then slowly warmed to room temperature. An aqueous NaOH solution (1.8 mL, 6.0 M) and H_2O_2 (1.8 mL, 35%) were then added and the mixture was left to warm up to room temperature for 5 h. H_2O (5 mL) was added and the aqueous layer was extracted with EtOAc (3×30 mL) and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (from hexane/EtOAc 7.5:1 to hexane/EtOAc 6:1) to give compound **26** (251 mg, 77%) as a colorless oil (**26**/**25**=98.7:1.3). The characterization of compounds **25** and **26** is reported above.

3.1.35. 2,2-Dimethyl-propionic acid {(1*R*,2*R*)-1-{(1*R*, 2*R*,6*R*)-2-[(2*R*)-2-(*tert*-butyl-diphenyl-silanyloxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enylmethyl}-2-methoxymethoxy-but-3-enyl} ester (40). Compound **26** (160 mg, 0.271 mmol) was dissolved in pyridine (1.8 mL). DMAP (4 mg, 0.03 mmol) and PivCl (161 mg, 1.33 mmol) were added and the mixture was stirred at room temperature for 18 h. EtOAc (9 mL) was added, the organic layer was washed with a saturated aqueous $KHSO_4$ solution (2×10 mL), the combined aqueous layers were back extracted with EtOAc (3×10 mL) and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 9:1) to give compound **40** (172 mg, 94%) as a colorless oil. R_f=0.71 (hexane/EtOAc 9:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.67–7.59 (m, 4H), 7.42–7.28 (m, 6H), 6.03–5.91 (m, 1H), 5.87–5.76 (m, 1H), 5.31–4.95 (m, 6H), 4.63 (d, J=6.7 Hz, 1H), 4.55 (d, J=6.7 Hz, 1H), 4.04–3.89 (m, 2H), 3.35 (s, 3H), 2.23–2.15 (m, 3H), 1.96–1.91 (m, 2H), 1.87–0.80 (m, 28H), 0.75 (d, J=6.7 Hz, 3H), 0.62 (d, J=6.7 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=173.7, 137.4, 135.9 (4C), 135.1, 134.9, 134.6, 134.3, 129.4, 129.3, 127.4 (2C), 127.3 (2C), 121.8, 119.2, 117.2, 94.3, 78.5, 71.8, 71.5, 55.7, 40.3, 37.2, 37.0, 35.8, 35.6, 29.7, 28.8, 27.3 (3C), 27.1 (4C), 24.3, 23.8, 21.0 (2C), 19.3; IR (CCl_4): ν=2935, 2905, 2867, 2830, 1728, 1431, 1372, 1159, 1107, 910; $[\alpha]_D^{20}$=+52.7 (c=0.77, EtOAc); HRMS (ESI): m/z: calcd for $C_{43}H_{64}NaO_5Si$: 711.4421 $[M+Na]^+$; found: 711.4406.

3.1.36. 2,2-Dimethyl-propionic acid {(1*R*,2*R*)-1-{(1*R*,2*R*,6*R*)-2-[(2*R*)-2-(*tert*-butyl-diphenyl-silanoxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enyl-methyl}-2-hydroxy-but-3-enyl} ester (41). Compound **40** (100 mg, 0.015 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and cooled to −78°C. Me_2S (42 mg, 0.068 mmol) and $BF_3{\cdot}Et_2O$ (11 mg, 0.079 mmol) were added and the solution was allowed to warm to −20°C for 0.5 h. Then, a saturated aqueous $NaHCO_3$ solution (1 mL) was added and the solution was warmed up to room temperature. The layers were separated, the aqueous layer was extracted with EtOAc (3×5 mL) and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 9:1) to give compound **41** (7 mg, 78%) as a colorless oil. R_f=0.40 (hexane/EtOAc 9:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.74–7.63 (m, 4H), 7.48–7.28 (m, 6H), 6.05–5.68 (m, 2H), 5.36–4.88 (m, 6H), 4.08–3.89 (m, 2H), 2.41–2.18 (m, 2H), 2.09–1.95 (m, 1H), 1.84–0.82 (m, 31H), 0.78 (d, J=6.7 Hz, 3H), 0.66 (d, J=6.7 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=178.3, 137.3, 137.1, 135.9 (4C), 135.1, 134.6 (2C), 129.5 (2C), 127.4 (4C), 121.7, 117.3, 116.3, 74.3, 73.1, 71.6, 40.5, 37.4, 36.7, 35.6, 35.3, 29.7, 28.7, 27.2 (3C), 27.1 (4C), 24.0, 23.7, 21.0 (2C), 19.3; IR (CCl_4): ν=3580, 3066, 2951, 2922, 2850, 1724, 1425, 1384, 1365, 1152, 1107, 905; $[\alpha]_D^{20}$=+70.7 (c=0.81, EtOAc); HRMS (ESI): m/z: calcd for $C_{41}H_{60}NaO_4Si$: 667.4159 $[M+Na]^+$; found: 667.4128.

3.1.37. 2,2-Dimethyl-propionic acid [(4*R*,4a*R*,6*R*,7*R*,11-*R*,12a*R*)-11-(*tert*-butyl-diphenyl-silanoxy)-7-hydroxy-4-isopropyl-1-methyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (42). Compound **41** (50 mg, 0.077 mmol) was dissolved in degassed CH_2Cl_2 (6.4 mL). Second generation RCM catalyst **13** (5.5 mg, 6 μmol) in

degassed CH_2Cl_2 (2.7 mL) was slowly added. The reaction mixture stirred for 12 h at room temperature. Additional RCM catalyst **13** (3 mg, 3.5 μmol) in degassed CH_2Cl_2 (1.5 mL) was slowly added and the mixture stirred for further 12 h at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 9:1) to provide unreacted **41** (15 mg) and compound **42** (29 mg, 60%, 86% considering the recovered starting material) as colorless oils. R_f=0.20 (hexane/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.66–7.63 (m, 4H), 7.44–7.32 (m, 6H), 6.10–5.91 (m, 2H), 5.75–5.70 (m, 1H), 5.55–5.49 (m, 1H), 5.14–5.05 (m, 2H), 4.40–4.36 (m, 1H), 4.30–3.80 (m, 4H), 2.81–2.73 (m, 1H), 2.38–2.25 (m, 2H), 2.15–2.10 (m, 1H), 1.82–1.10 (m, 16H), 1.06 (s, 9H), 0.85 (d, J=6.8 Hz, 3H), 0.67 (d, J=6.8 Hz, 3H); ^{13}C NMR (100.8 MHz, $CDCl_3$): δ=173.9, 136.3, 135.9 (2C), 135.8 (2C), 133.9 (2C), 130.3, 129.8, 129.7, 127.7, 127.6 (2C), 127.5 (2C), 119.3, 75.3, 73.1, 72.3, 37.2, 36.5, 35.1, 34.7, 30.5, 27.7, 27.2 (3C), 27.0 (3C), 26.4, 24.4, 22.7, 21.0 (2C), 20.8, 19.2; IR (CCl_4): ν=3618, 3070, 2955, 2923, 2850, 1725, 1477, 1459, 1425, 1384, 1365, 1155, 1100, 1080; $[\alpha]_D^{20}$=+4.0 (c=0.35, EtOAc); HRMS (ESI): m/z: calcd for $C_{39}H_{56}NaO_4Si$: 639.3846 $[M+Na]^+$; found: 639.3860.

3.1.38. 2,2-Dimethyl-propionic acid [(4*R*,4a*R*,6*R*,7*R*,11-*R*,12a*R*)-11-(*tert*-butyl-diphenyl-silanyloxy)-4-isopropyl-7-methoxy-1-methyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (43). Compound **42** (10 mg, 0.016 mmol) was dissolved in CH_2Cl_2 (0.2 mL). 2,6-Di-*tert*-Butyl-pyridine (31 mg, 0.16 mmol) and MeOTf (13 mg, 0.08 mmol) were added and the solution was stirred for 7 h at 40°C. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 9:1) to give compound **43** (10 mg, 99%) as a colorless oil. R_f=0.66 (hexane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.66–7.64 (m, 4H), 7.51–7.34 (m, 6H), 6.14–5.60 (br s, 2H), 5.06 (br s, 2H), 3.97 (br s, 1H), 3.71 (m, 1H), 3.25 (s, 3H), 2.77 (m, 1H), 2.20 (m, 1H), 2.07–0.95 (m, 31H), 0.83 (d, J=6.7 Hz, 3H), 0.65 (d, J=6.5 Hz, 3H); ^{13}C NMR (100.8 MHz, $CDCl_3$): δ=183.1, 135.9, 135.8 (4C), 134.1, 134.0, 130.2, 129.7, 129.6, 128.3, 127.6 (2C), 127.5 (2C), 119.0, 115.1, 80.8, 73.2, 72.4, 56.9, 50.5, 38.5, 37.5, 37.2, 36.3, 30.1 (3C), 27.0 (3C), 26.4, 24.8, 24.3, 22.6, 21.0, 19.2; IR (CCl_4): ν=2962, 2935, 2901, 2867, 2293, 2000, 1729, 1558, 1429, 1368, 1261, 1160; $[\alpha]_D^{20}$=−23.5 (c=1.00, EtOAc); HRMS (ESI): m/z: calcd for $C_{40}H_{58}O_4Si$: 631.4183; found: 631.4200.

3.1.39. 2,2-Dimethyl-propionic acid [(4*R*,4a*R*,6*R*,7*R*,11-*R*,12a*R*)-11-hydroxy-4-isopropyl-7-methoxy-1-methyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (44). Compound **43** (10 mg, 0.016 mmol) was dissolved in THF (0.40 mL) and TBAF (0.034 mL, 0.034 mmol, 1.0 M in THF) was added. The reaction mixture stirred 14 h at room temperature. An aqueous phosphate buffer solution (1.0 mL, pH=7) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3×5 mL) and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc 8:2) to yield compound **44** (4 mg, 67%) as a colorless oil. R_f=0.10 (hexanes/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.97 (dt, J=16.5, 4.6 Hz, 1H), 5.85 (m, 1H), 5.65 (br s, 1H), 5.24 (br s, 1H), 4.08 (m, 1H), 3.74 (dd, J=9.0, 7.4 Hz, 1H), 3.29 (s, 3H), 2.98 (m, 1H), 2.39 (m, 1H), 1.88–1.19 (m, 23H), 0.85 (d, J=6.8 Hz, 3H), 0.68 (d, J=6.8 Hz, 3H); ^{13}C NMR (100.8 MHz, $CDCl_3$): δ=177.7, 144.6, 132.2, 129.1, 119.8, 80.8, 72.3, 72.1, 57.0, 37.5, 37.2, 36.5, 34.9, 31.5, 30.2, 27.2, 27.1 (3C), 26.5, 24.4, 23.2, 21.0 (2C); IR (CCl_4): ν=3622, 3019, 2961, 2932, 2904, 2874, 2291, 2004, 2003, 1848, 1729, 1558, 1480, 1461, 1397, 1388, 1369, 1283, 1255, 1218, 1159, 1107; $[\alpha]_D^{20}$=−62.6 (c=0.70, EtOAc); HRMS (ESI): m/z: calcd for $C_{28}H_{46}O_5$: 393.3005; found: 393.3015.

3.1.40. (*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid [(1*R*,4a*R*,6*R*,10*R*,11*R*,12a*R*)-11-(2,2-dimethyl-propionyloxy)-1-isopropyl-10-methoxy-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (45). Compound **44** (7 mg, 0.018 mmol) was dissolved in $ClCH_2CH_2Cl$ (1.0 mL) and added to mixed anhydride **16** (prepared according to Ref. 6b; 120 mg, 0.509 mmol). NEt_3 (33 mg, 0.325 mmol) and DMAP (2 mg, 0.0164 mmol) were added and the solution stirred for 64 h at room temperature and refluxed for 2 h. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (from 100% hexanes to hexanes/EtOAc 1:4) to yield compound **45** (7 mg, 79%) as a colorless oil. R_f=0.23 (hexane/EtOAc 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.53 (d, J=15.6 Hz, 1H), 7.46 (s, 1H), 7.06 (s, 1H), 6.53 (d, J=15.6 Hz, 1H), 5.99–5.41 (br s, 2H), 5.94 (dt, J=16.1, 4.5 Hz, 1H), 5.32–5.00 (br s, 2H), 3.76 (t, J=7.7 Hz, 1H), 3.70 (s, 3H), 3.28 (s, 3H), 3.04 (m, 1H), 2.46 (m, 1H), 2.17–1.19 (m, 20H), 0.89 (m, 2H), 0.84 (d, J=6.7 Hz, 3H), 0.69 (d, J=6.7 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=176.9, 166.6, 138.7, 138.6, 136.0, 135.9, 132.4, 129.2, 122.3, 80.8, 74.0, 72.4, 56.9 (2C), 37.6, 36.3, 33.5 (2C), 30.2, 27.1 (3C), 26.6 (3C), 24.4, 23.1, 21.0 (2C); IR (CCl_4): ν=2961, 2932, 2873, 2821, 2291, 2003, 1848, 1729, 1708, 1646, 1544, 1480, 1461, 1387, 1253, 1217, 1159; $[\alpha]_D^{20}$=− 43.8 (c=0.70, EtOAc); HRMS (ESI): m/z: calcd for $C_{31}H_{46}N_2O_5$: 527.3485 $[M+H]^+$; found: 527.3499.

3.1.41. 2,2-Dimethyl-propionic acid {(4*R*,4a*R*,6*R*,7*R*,11-*R*,12a*R*)-11-(*tert*-butyl-diphenyl-silanyloxy)-4-isopropyl-1-methyl-7-[(2′*)-tetrahydro-pyran-2′-yloxy)]-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl} ester (46). Compound **42** (20 mg, 0.032 mmol) was dissolved in CH_2Cl_2 (0.3 mL). Dihydropyran (4 mg, 0.048 mmol) and PPTS (1 mg, 0.005 mmol) were added and the solution was stirred for 12 h at room temperature. *i*-Pr_2O (5 mL) was added, the organic layer was washed with a semisaturated NaCl solution (2×5 mL) and the organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 14:1) to yield compound **46** (20 mg, 91%) as a colorless oil. R_f=0.40 (hexane/EtOAc 14:1); ^{1}H NMR (250 MHz, $CDCl_3$, signal doubling due to diastereomers): δ=7.68–7.64 (m, 4H), 7.44–7.34 (m, 6H), 6.20+6.02 (m, 1H), 5.86+5.70 (m, 2H), 4.80–4.60 (m, 2H), 4.07–3.92 (m, 1H), 3.90–3.75 (m, 1H), 3.50–3.35 (m, 1H), 2.90–2.75 (m, 1H), 2.35–2.20 (m, 1H), 2.20–2.10 (m, 1H), 1.95–1.05 (m, 36H), 0.84 (d, J=6.7 Hz, 3H), 0.66–0.63 (m,

3H); ^{13}C NMR (50.3 MHz, $CDCl_3$, signal doubling due to diastereomers): δ=178.0, 135.9+135.8, 131.0+134.1 (2C), 130.0, 129.7+129.6 (2C), 128.3, 127.6+127.5 (4C), 119.0, 100.7+93.4, 78.4+77.2, 73.3+72.7, 68.6, 62.1+60.8, 38.6, 37.1, 36.4+36.3, 34.8, 30.5+30.4, 27.4, 27.2, 27.1 (2C), 27.0, 26.4, 25.5+25.4, 24.8, 24.4, 22.9+22.7, 21.0+20.7, 19.2+19.1, 18.3; IR (CCl_4): ν=3072, 3052, 2961 2859, 2290, 2003, 1848, 1742, 1728, 1558, 1480, 1462, 1428, 1390, 1371, 1261, 1219, 1159, 1105, 1011; $[\alpha]_D^{20}$=−2.8 (c=8.75, EtOAc); HRMS (ESI): m/z: calcd for $C_{44}H_{64}NaO_5Si$: 723.4421 $[M+Na]^+$; found: 723.4420.

3.1.42. 2,2-Dimethyl-propionic acid {(4*R*,4a*R*,6*R*,7*R*,11*R*,12a*R*)-11-hydroxy-4-isopropyl-1-methyl-[(2′*)-7-(tetrahydro-pyran-2′-yloxy)]-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl} ester (47). Compound **46** (18 mg, 0.025 mmol) was dissolved in THF (1.5 mL) and TBAF (125 μL, 0.125 mmol, 1.0 M in THF) was added. The reaction mixture was stirred 12 h at room temperature. An aqueous phosphate buffer solution (1.0 mL, pH=7) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3×5 mL) and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc 8:2) to yield compound **47** (11 mg, 96%) as a colorless oil. R_f=0.11 (hexanes/EtOAc 8:2); ^{1}H NMR (200 MHz, $CDCl_3$, signal doubling due to diastereomers): δ=6.04–5.91 (m, 1H), 5.85 (dt, J=12.2, 4.5 Hz, 1H), 5.73 (m, 2H), 5.24 (br s, 2H), 4.90–4.62 (m, 2H), 4.39–4.25 (m, 1H), 4.20–3.97 (m, 1H), 3.97–3.77 (m, 1H), 2.55–2.39 (m, 1H), 3.10–2.95 (m, 1H), 2.50–2.27 (m, 1H), 2.15 (br s, 1H), 2.00–1.15 (m, 27H), 0.85 (d, J=6.8 Hz, 3H), 0.69+0.67 (d, J=6.8 Hz, 3H); ^{13}C NMR (100.8 MHz, $CDCl_3$, signal doubling due to diastereomers): δ=139.7, 132.8, 130.8, 129.6, 128.9, 119.6, 100.4+93.3, 78.1, 73.0, 72.5+72.0 (2C), 68.1+60.7, 37.5, 37.2, 37.0 (2C), 36.5, 34.8, 30.6, 30.4+30.3, 27.3, 27.1 (3C), 26.3, 25.4, 24.8, 24.4, 23.2, 21.0 (2C), 20.7, 18.9+18.2; IR (CCl_4): ν=3622, 3449, 2961, 2931, 2873, 2290, 2003, 1848, 1728, 1558, 1480, 1460, 1441, 1397, 1388, 1369, 1322, 1261, 1218, 1159, 1099, 1014, 978; $[\alpha]_D^{20}$=−64.3 (c=1.04, EtOAc); HRMS (ESI): m/z: calcd for $C_{28}H_{46}O_5+NH_4$: 480.3689 $[M+NH_4]^+$; found: 480.3690.

3.1.43. 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid {(1*R*,4a*R*,6*R*,10*R*,11*R*,12a*R*)-11-(2,2-dimethyl-propionyloxy)-1-isopropyl-4-methyl-10-[(2′*)-(tetrahydro-pyran-2-yloxy)]-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl} ester (48). Compound **47** (10 mg, 0.022 mmol) was dissolved in $ClCH_2CH_2Cl$ (1.2 mL) and added to mixed anhydride **16** (prepared according to Ref. 6b; 190 mg, 0.807 mmol). NEt_3 (41 mg, 0.402 mmol) and DMAP (2.5 mg, 0.020 mmol) were added and the solution was stirred for 40 h at room temperature and 3 h at 50°C. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 1:4) to yield compound **48** (10 mg, 75%) as a colorless oil. R_f=0.23 (hexane/EtOAc from 1:3 to 1:2); ^{1}H NMR (400 MHz, $CDCl_3$, signal doubling due to diastereomers): δ=7.63+7.52 (d, J=15.5 Hz, 1H), 7.49+7.48 (s, 1H), 7.16+7.06 (s, 1H), 6.55+6.53 (d, J=15.5 Hz, 1H), 6.09+5.75 (m, 4H), 5.24 (s, 2H), 4.85–4.65 (m, 2H), 4.40–4.29 (m, 1H), 4.10–3.97 (m, 1H), 3.90–3.77 (m, 1H), 3.72+3.70 (s, 3H), 3.55–3.39 (m, 2H), 3.20–3.05 (m, 1H), 2.61–2.50+2.49–2.35 (m, 1H), 2.21 (br s, 1H), 2.10–1.15 (m, 23H), 2.17–1.38 (m, 15H), 0.84+0.83 (d, J=6.8 Hz, 3H), 0.75–0.64 (m, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$, signal doubling due to diastereomers): δ=178.1, 166.6, 139.7, 138.4, 135.8+135.7, 131.1, 129.9, 123.9, 122.4, 116.5, 114.6, 100.3+93.5, 78.2, 73.2, 72.7, 70.3, 61.7+60.8, 38.5, 37.4, 36.3, 36.1, 34.4, 33.7, 33.6 (3C), 30.5, 27.3 (3C), 27.2, 27.1, 26.6, 26.5, 26.4, 23.2, 21.0, 18.5+18.0; IR (CCl_4): ν=2961, 2873, 1727, 1708, 1645, 1480, 1460, 1387, 1368, 1159, 1159, 909; $[\alpha]_D^{20}$=−23.6 (c=0.32, EtOAc); HRMS (ESI): m/z: calcd for $C_{32}H_{53}N_2O_6$: 597.3904 $[M+H]^+$; found: 597.3909.

3.1.44. 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid [(1*R*,4a*R*,6*R*,10*R*,11*R*,12a*R*)-11-(2,2-dimethyl-propionyloxy)-10-hydroxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (49). Compound **48** (13 mg, 0.022 mmol) was dissolved in EtOH (1.5 mL, 80%). PTSA (1 mg, 0.0049 mmol) was added and the solution was stirred for 4 days at room temperature. EtOAc (5 mL) was added, the organic layer was washed with a saturated aqueous $NaHCO_3$ solution (2×5 mL), with a saturated aqueous NaCl solution (5 mL) and then the organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexanes/EtOAc, 1:5) to yield compound **49** (5 mg, 40%) as a colorless oil. R_f=0.23 (hexanes/EtOAc, 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.91 (s, 1H), 7.50 (d, J=15.6 Hz, 1H), 7.10 (s, 1H), 6.68 (d, J=15.6 Hz, 1H), 6.09–5.61 (m, 3H), 5.37–5.13 (m, 2H), 4.93–4.66 (m, 1H), 3.78 (s, 3H), 3.60–3.37 (m, 1H), 4.23–3.02 (m, 1H), 2.67–1.07 (m, 23H), 0.84 (d, J=5.2 Hz, 3H), 0.67 (d, J=5.2 Hz, 3H); ^{13}C NMR (100.8 MHz, $CDCl_3$): δ=178.7, 166.3, 140.5, 136.4, 135.1, 131.8, 121.3, 119.2, 78.0, 73.1, 70.2, 69.0, 37.1, 36.2, 33.4, 30.4, 27.3 (2C), 27.1, 26.4, 24.4, 23.2, 22.9, 22.8; IR (CCl_4): ν=3405, 3135, 3022, 2960, 2991, 1708, 1646, 1542, 1480, 1442, 1387, 1369, 1298, 1262, 1115, 1024, 909; $[\alpha]_D^{20}$=−35.5 (c=0.23, EtOAc); HRMS (ESI): m/z: calcd for $C_{30}H_{45}N_2O_5$: 513.3328 $[M+H]^+$; found: 513.3337.

3.2. Tubulin polymerization assay

The samples were prepared directly in 1.5 mL optical glass cuvettes at 0°C which contained aqueous 'Mes buffer' [0.900 mL (0.1 M MES, 1 mM EGTA, 0.5 mM $MgCl_2$, pH=6.6)], GTP (10 μL, 100 mM in doubly distilled water) and tubulin (100 μL, 8–10 mg/mL of aqueous 'Mes buffer'). The cuvettes were thoroughly agitated and immediately placed in a spectrophotometer, preheated at 37°C, alongside a blank sample containing aqueous 'Mes buffer' (0.990 mL) and GTP (10 μL, 100 mM in doubly distilled water) and the absorbance at λ=350 nm was recorded. When the absorbance reached a plateau (after 15 min), $CaCl_2$ (10 μL, 400 mM in doubly distilled water) was added to each cuvette. After another 15 min, a minimum absorbance was reached and the tubulin-polymerizing-agent in DMSO (2.5 mM) was added to the cuvettes in portions (2, 2, 4, 12, 20 and 40 μL) every 15 min and thoroughly shaken to give final concentrations of 0.5, 1.0, 2.0, 5.0, 10 and 20 μM, respectively (final concen-

trations of the tubulin-polymerizing-agent in the assay). The results were compared to the untreated control (using the same quantities of DMSO without the tubulin-polymerizing-agent) to assess the relative change in absorbance due to microtubule assembly. The results are presented as ED_{50} and ED_{90} which correspond to the dose of tubulin-polymerizing-agent required to induce 50 and 90% microtubule assembly (MES, 2-(morpholino)ethane sulphonic acid; EGTA, ethyleneglycol-bis-(β-aminoethylether)-*N*,*N*,*N*′,*N*′-tetraacetic acid; GTP, guanosine 5′-triphosphate).

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